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NEW DIURETICS AND ANTIHYPERTENSIVE AGENTS

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NEW DIURETICS AND ANTIHYPERTENSIVE AGENTS*

Conference Chairman and Editor

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PRESENT CONCEPTS OF THE MECHANISM OF URINE FORMATION AND OF DIURETIC ACTION*

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Traditionally, diuretics have been considered drugs that increase the volume of the urine.[1] However, the dependence of the rate of excretion of water on the elimination of sodium in the urine and the effectiveness of salt depletion in the therapy of hypertension have centered attention on the natriuretic action of the diuretics rather than on their effect on the volume of the urinary output. Although many drugs and procedures may exert a diuretic or natriuretic action, the most potent of the diuretic drugs exert their effect by direct action on normal renal function. To understand their action, therefore, we must consider first the mechanisms concerned in the formation of the urine.

In the normal person the kidneys maintain a constant composition, volume, and osmolarity of the extracellular fluid. Hence, the administration of an excessive amount of water or other substance not metabolized in the body and excretable by the kidneys results in diuresis. Water thus constitutes an effective diuretic in the normal patient when one desires only to increase the volume of the urine. The addition of certain salts, designated as osmotic diuretics, such as potassium salts and urea, accentuates the diuretic action of water. Under these conditions diuretic action involves only normal renal functions that respond to maintain homeostasis. Our chief interest in diuretics centers on agents that actively modify renal function and thus lead to the excretion of salt and water retained in the body. Such retention may be a consequence either of the direct effects of disease on the kidney or peripheral tissues or of indirect effects induced by the primary disturbance on normal renal function.

The Mechanism of Urine Formation

The kidney is composed of units designated as nephrons, each of which, although differing somewhat from the others, depending on their location in the kidney, may for simplicity be considered representative of the action of the kidney as a whole. Each of the million or more nephrons present in the human kidney consists of a glomerulus, proximal tubule, thin loop of Henle, distal tubule, and collecting duct; we may consider the action of each of these morphologic divisions successively, as they participate in the elaboration of the urine.

Glomerular filtration. It is generally conceded that the glomeruli serve as ultrafilters permitting the passage of the prodigious amount of approximately 180 l. of glomerular filtrate daily, or about 0.07 ml. through each glomerulus. The glomerular filtrate contains all of the crystalloids present in the blood plasma (such as glucose, chloride, sodium, potassium, urea, phosphate, and creatinine), and only trivial amounts of its colloidal constituent (protein). The classic experiments of Richards and his collaborators,[2] made by direct analysis

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of the glomerular filtrate, demonstrated that this fluid represents a true ultrafiltrate comparable to that obtained by filtration of plasma through a semipermeable membrane. All 180 l. of glomerular filtrate are reduced in volume during their passage through the tubule and are altered in composition to form the 1 to 1.5 l. of urine that appear ultimately in the bladder. Conservation of the water and essential solutes that appear in the glomerular filtrate constitutes a vital renal function. The production of glomerular filtrate is accomplished by the mechanical action of the heart in maintaining an adequate pressure gradient in the glomerular tuft; the conversion of this filtrate into urine is dependent on renal activity.

Moderate changes in the total renal blood flow do not affect materially the kidney function. It is probable, however, that minor changes in the medullary blood flow, which constitutes normally only about 10 per cent of the total renal blood flow and hence is undetectable by available methods of mesurement, may be of great importance in maintaining normal renal function.[3] This is particularly pertinent if we consider the importance of the medullary circulation in the countercurrent process (discussed in another section). Such minor alterations in medullary blood flow may indeed constitute an important mechanism whereby the ill-defined factors responsible for regulating the volume and composition of the extracellular fluid are mediated.

Action of the proximal tubule. The glomerular filtrate, as it passes through the straight and convoluted proximal segment of the tubule, is reduced to less than one third of its original volume. This reduction in volume is believed to be accomplished by the active reabsorption of sodium, the tubular cells acting as a "sodium pump" to transfer the ion from the lumen into the peritubular space, from which it returns to the circulation. This active transfer of cation is accompanied by the concomitant transfer of anion, maintaining electric neutrality of potassium, and of other threshold substances. Since the proximal tubule is freely permeable to water, the transfer of electrolyte will be accompanied by the passive transfer of water, so that the fluid in the proximal tubule remains iso-osmotic with plasma despite its great reduction in volume.[4]

The nature of the transport mechanism responsible for the transfer of sodium from the lumen to the peritubular space of the proximal tubule is not known. However, it must be remembered that all tissue cells contain sodium in a concentration much less than that in the surrounding extracellular fluid and hence must have a mechanism for the extrusion of this cation that enters the cells. If it is assumed that the membrane of the tubular cells bordering the lumen is highly permeable to sodium, these cells may extrude the sodium into the peritubular space by the same fundamental process that maintains the sodium content of other body cells at their low level. Such a process probably takes place with a varying degree of effectiveness throughout the length of the tubule, including the collecting duct. Whether other active transfer mechanisms exist for other ions or whether these ions move as a consequence of, for example, the movements of sodium or of special ion-exchange mechanisms remains to be established.[3,4]

The *p*H of the glomerular filtrate is not altered materially in its passage through the proximal tubule, except under conditions of marked osmotic diuresis induced, for example, by the infusion of concentrated glucose or mannitol.

The chief site of acidification of the urine is in the distal tubule and, possibly, in the collecting duct, although the proximal tubule probably also can participate in this process.

The fluid leaving the proximal tubule contains sodium, chloride, and bicarbonate in the same concentration as in the plasma, these ions being reabsorbed from the glomerular filtrate in equivalent amounts. Glucose, potassium, amino acids, vitamins, and other so-called threshold constituents of the plasma are more or less completely reabsorbed, accompanied by water that passes by passive diffusion to maintain the isotonicity of the residual fluid. Of the 118 ml. of water appearing each minute in the glomerular filtrate, only about 35 ml. remain to enter the loop of Henle. Such excretory products as urea, creatinine, and uric acid are not concentrated in the proximal segment to a degree comparable to the reabsorption of water; they diffuse back across the tubular epithelium and are only moderately concentrated in this portion of the tubule.[5]

An alternative hypothesis to that just described as accounting for the changes occurring in the proximal tubule assumes the passive reabsorption of sodium, chloride, bicarbonate, and water as a consequence of the osmotic forces exerted by the plasma proteins and those generated as a result of the active reabsorption of glucose, amino acids, and other threshold constituents of the plasma. Such forces obviously will contribute to the reabsorptive process in the proximal tubule, but whether they suffice to account for the magnitude and speed of the observed changes is questionable.[5]

Function of the loop of Henle. The loop of Henle, which receives the residual fluid from the proximal tubule, is present only in birds and mammals, which alone are capable of forming a hypertonic urine. It was for a time believed, therefore, that concentration of the urine occurred primarily in this segment of the kidney and that the transport of water occurred here under the influence of the antidiuretic hormone of the pituitary. This view has now been discredited by the demonstration that fluid collected from the distal convoluted tubule is isotonic or hypotonic but never hypertonic to plasma. The formation of a hypertonic urine must accordingly occur at a point beyond the loop of Henle, namely, in the distal tubule and the collecting duct.[3,5]

A new concept of the mechanism whereby isotonic fluid from the proximal tubule is concentrated to form urine has been presented by Wirtz *et al.*[6] and elaborated and confirmed by several groups of investigators.[3,7-9] According to present concepts, the loops of Henle, collecting ducts, blood capillaries, and intervening interstitial tissue of the medulla are functionally as well as anatomically interrelated. This unique relationship makes possible the application of a countercurrent multiplier system, whereby relatively minor changes in concentration permit the establishment of the major alterations in osmolarity that occur in the formation of the urine.

The nature of the exchanges occurring between the lumen and the peritubular space of the loop of Henle is still a matter of controversy.[3] Since the fluid increases in osmolarity as it descends the loop, and decreases in osmolarity as it ascends the loop, it has been suggested that sodium is transferred from lumen to interstitium by an active transfer process in the ascending limb of the loop and that it passes by simple diffusion from peritubular space to lumen in the descending loop. The epithelium of the ascending limb is believed to be impermeable, while the descending limb is assumed to be permeable to water. Consequently the tubular fluid will become more hypertonic as it progresses through the descending limb of the loop and increasingly hypotonic as it passes through the ascending limb.[5]

The above-described course of events assumes that there are differences in action of morphologically similar segments of the nephron. Since this is unlikely, it appears more logical to assume that the thicker portions of the loop function in a manner similar to their contiguous proximal and distal tubular cells. Even the cells of the thin portion of the loop may, like other cells of the body, share the ability to extrude sodium from the lumen to the peritubular space. The alteration in osmolarity of the fluid as it traverses the loop is a consequence of the still incompletely defined countercurrent multiplier system, in the operation of which urea and other urinary constituents must also play important roles.

Little attention has been given to the changes in osmolarity induced by the passage of urea across the tubule, although it has been suggested that equilibration of this crystalloid between the lumen and interstitium may be an important function of the thin portion of the loop of Henle.[7,8] The effect of this exchange of urea and water acting through the countercurrent multiplier system may be enough to account for the observed changes in the osmolarity of the fluid as it passes through the loop of Henle, without the less likely assumption that various parts of the loop act qualitatively differently.

The countercurrent multiplier system. According to the now generally accepted concept of the countercurrent multiplier system as applied to the kidney, the contents of the loops of Henle, capillaries, and collecting ducts influence one another through the mediation of the medullary interstitial tissue. The application of this principle assumes the maintenance of a state of maximal hypertonicity in the interstitial tissue at the lower end of the loop, with a gradual diminution in tonicity from the papillary tips of the medulla to the corticomedullary junction, in which the proximal and distal convolutions are located.[6] This hypertonicity of the medullary interstitium is maintained by the active transfer of sodium and other ions across the loop of Henle.

Of particular interest have been the results obtained with the desert rat, a rodent capable of producing a urine highly hypertonic compared to that of other mammals. In this animal the renal papilla, which comprises a long projection into an enlarged pelvis, consists of thin segments of loops of Henle interspersed with collecting ducts and capillary loops. It is thus especially well adapted for the application of the countercurrent multiplier system.[10]

The medullary tissue, in which the countercurrent multiplier system is presumed to operate, must be significantly hypertonic to blood plasma and to the cortex of the kidney. That this is the case has been demonstrated by the fact that slices of medullary tissue contain increasing amounts of sodium, chloride, and urea,[7-9] progressing from the corticomedullary junction to the tip of the papilla. The osmotic pressure of such slices also increases progressively, reaching a maximum at the tip of the papilla, and blood collected from surface capillaries of the papilla is hypertonic to the systemic blood.[6,9] The last-named observation is important since, obviously, the circulation through the medulla plays an integral role in the countercurrent multiplier system.[10]

Function of the distal tubule. The fluid entering the distal tubule is iso-osmotic or hypotonic, depending on the magnitude of the exchange of water and solute between cells and interstitium during its passage through the loop of Henle. Reabsorption of sodium, which continues in the distal tubule, reduces its concentration to a low value. In the maximally hydrated animal, a minimal amount of antidiuretic hormone is made available, and the collecting ducts and distal tubules are relatively impermeable to water. In the hydropenic state, on the other hand, the availability of circulating antidiuretic hormone in high concentration renders the distal and collecting tubules more permeable to water, and the hypotonic urine entering the distal tubule is concentrated as it traverses the collecting ducts.

The reabsorption of water in the distal tubule and collecting ducts is accomplished by passive transfer to the hyperosmolar medium of the interstitium, accentuated by the osmotic force generated by the active transfer of sodium and other solutes that occurs in this area. It is generally agreed that there is no need for assuming the existence of an active transport mechanism for water in the tubule, this solvent moving only in response to osmotic forces generated by the transfer of solutes across membranes, the permeability of which is altered by the humoral mediation of the antidiuretic hormone of the neurohypophysis.

The distal tubule is also the chief site of elimination of acid, which is necessary for maintaining the acid-base balance of the organism. This is accomplished by the exchange of hydrogen ions (available from H_2CO_3 and from NaH_2PO_4) for sodium ions, by the reabsorption of $NaHCO_3$, and by the production of NH_3 from glutamine by glutaminase. Agents that inhibit carbonic anhydrase induce acidosis and act as diuretics by disturbing this exchange of sodium for hydrogen, thus rendering the latter unavailable. Potassium also is secreted by the distal tubule by an exchange reaction with sodium, and some of the newer diuretics, by accelerating potassium excretion, may not only induce a hypokalemia of serious degree but also dislocate the normal acid-base relationships.[5,10] The administration of large doses of potassium, on the other hand, will result in a competition of K^+-for-H^+ exchange, leading to the formation of an alkaline urine. Because of these interrelationships in the excretion of ions, some dislocation of electrolyte balance by diuretics is inevitable. One can only minimize such undesirable effects or counteract them, for example, by the administration of extra potassium, when the loss of this ion is undesirable.

Function of the collecting ducts. The collecting ducts of the tubule, in the light of recent studies, have attained an importance more consonant with their morphologic appearance than was formerly the case, when they were considered as relatively inert collecting conduits. The most recent evidence seems to indicate, in fact, that they act functionally as part of the distal tubule and participate probably in the reabsorption of sodium, acidification of the urine, and other activities in which the distal tubule is concerned.[7]

The collecting ducts constitute an integral part of the countercurrent multiplier system and play a major role in the concentration of the urine.[3] Because of their permeability to water and the hypertonicity of the fluid with which they are surrounded, water passes by osmotic attraction from the lumen into the interstitium. This transfer of water is dependent upon the availability of the antidiuretic hormone, in the absence of which the kidney is unable to form a concentrated urine.

Hormonal control of renal function. The kidney, like other organs, is dependent upon the integrity of normal endocrine function. The depression of glomerular blood flow induced by pituitary or adrenal cortical insufficiency results, accordingly, in a delayed renal response to water and salt loads. Thyroid insufficiency likewise results in a generalized accumulation of fluid, which is excreted during the diuresis that follows treatment with thyroid hormone. More specific and direct examples of the action of endocrine organs on renal function are found in the effect of the adrenal cortex on the control of water and electrolyte metabolism and in that of the antidiuretic hormone of the neurohypophysis on the conservation of water by the kidney.[1]

The antidiuretic hormone acts to render the distal and collecting tubules permeable to water, thereby permitting concentration of the urine as it passes through this part of the nephron. It acts presumably by the same mechanism whereby it renders the frog's skin and bladder permeable to water when the hormone is added to the medium in which these tissues are suspended. One would anticipate that a drug that antagonized the action of the antidiuretic hormone would serve as a potent diuretic, but such an agent is not available. The diuretic action of alcohol and certain other drugs is believed to be dependent on their altering the rate of excretion of the antidiuretic hormone.

The mineralocorticoids, of which aldosterone is believed to represent the physiological hormone, act to retain sodium and excrete potassium by acting on the distal tubule. In adrenal cortical insufficiency there is a loss of sodium and accumulation of potassium, which leads to many of the important symptoms induced by adrenalectomy. Nephrectomy prevents such manifestations, and adrenalectomized dogs, which normally survive only for four or five days, may be maintained in relatively good condition for a month without recourse to hormonal therapy, if one maintains their renal excretory function and electrolyte and water balance by peritoneal lavage.[11]

The role of aldosterone in the dislocation of electrolyte and water metabolism observed in such conditions as heart failure, cirrhosis of the liver, and hypertension, in which the use of diuretics is indicated, has not been established with certainty. Aldosterone antagonists exert a diuretic action by antagonizing not only the action of any increased aldosterone produced in disease but also that which is normally secreted. Depression of adrenocorticotropin secretion by the pituitary, or direct inhibition of the synthesis of hormones by the adrenal cortex, will also result in the renal loss of sodium and water and the retention of potassium. The glucocorticoids, when administered in large doses or produced endogenously, as in Cushing's disease, induce edema as a consequence of their sodium-retaining action.

Pathogenesis of Edema and Sodium Retention

Although the factors concerned in the production of edema and sodium retention are beyond the scope of the present paper, a brief consideration of these factors is essential for understanding the mechanism of action of the diuretics.

The underlying disturbance responsible for the edema of congestive heart failure, nephrosis, or the nephrotic stage of chronic nephritis, for the localized accumulation of ascitic fluid in hepatic cirrhosis, or for sodium retention in hypertensive cardiovascular disease are of diverse origin. It is not surprising that the effectiveness of different diuretics will vary with the condition under treatment.

Except for intracellular edema due to water excess, in which abstention from water relieves the underlying condition, most instances of edema are extracellular and involve the retention of an excess of sodium as well as water. In these, as well as in the localized accumulation of ascitic fluid in cirrhosis, and in the dislocation of electrolyte balance observed in the hypertensive person, dietary restriction of sodium will remedy the abnormal state of sodium retention. However, the difficulty of applying this procedure in practice renders the use of diuretic drugs either alone or, preferably, in combination with moderate sodium restriction, desirable.

The fundamental action of the kidney in electrolyte and water metabolism is concerned with the conservation of the large amounts of these vital constituents of the organism that appear in the glomerular filtrate. The predominant effect of renal dysfunction would be anticipated, therefore, to result in acidosis and azotemia with dehydration and electrolyte deficiency rather than with edema and salt retention. It is not surprising, therefore, that patients may suffer from severe degrees of kidney damage, as encountered in the late stages of chronic nephritis and, although manifesting marked azotemia and acidosis, may not be edematous. In the presence of normal renal excretory function as encountered in congestive heart failure or essential hypertension, a disturbance in water and electrolyte metabolism of a sufficient degree to induce edema or sodium retention is apparently a result primarily of extrarenal mechanisms that act on the kidney and alter its normal homeostatic function.

Since the retention of excessive salt and water ultimately devolves upon the kidney, any drug that will accelerate the excretion of salt will relieve the edema, regardless of the mechanisms responsible for its accumulation. It is difficult in our present state of knowledge to assign with accuracy the relative importances of various factors responsible for abnormal fluid and electrolyte accumulations. However, unquestionably many factors are involved and, since the diuretics act by different mechanisms, the success with any particular one will depend upon the factors responsible for the abnormal state that is being treated.

It is generally accepted that the initiating factor in inducing the edema of congestive heart failure is a decline in cardiac output, which is accompanied by a decrease in the effective renal blood flow and a decrease in glomerular filtration rate. Increased venous and capillary pressures will cause an increased transudation of fluid and its accumulation in the tissues. In addition to these factors, the adrenal and neurohypophyseal hormones are called into play as a homeostatic mechanism for increasing blood volume. The appearance of edema accordingly may represent in part an undesirable and harmful compensatory reaction, comparable to the anaphylactic response in the antigen-antibody reaction.

Among the extrarenal factors that participate in the formation and localization of edema are those concerned with the exchange of fluid between the capillaries and tissues. An increase in capillary pressure with a dislocation of the Starling equilibrium or a decrease in oncotic pressure of the plasma, as occurs in the hypoproteinemia of nephrosis or nutritional edema, will cause an accumulation of edema fluid. Local variations in tissue turgor will determine the localization of the edema, as will such processes as increased portal pressure, venous obstruction, or changes in vascular permeability induced by a loss of the integrity of the capillary endothelium.

The nature and pathogenesis of the dislocation in salt and water metabolism observed in hypertensive cardiovascular disease remains unclear.

Action of Diuretics

The most effective of the available diuretics exert their action by inhibiting the reabsorption of sodium by the kidney. Sodium restriction will induce similar effects but is slower in action and must be drastic to be effective, particularly in the management of hypertension. Moderate restriction of sodium is always desirable as an adjuvant measure because it minimizes the dose of the diuretic required to elicit the desired effects.

In the therapeutic use of diuretics it is essential to utilize such measures as may overcome the factors that evoke the kidney changes responsible for the excessive retention of salt and water. Thus patients may appear to be refractory to a diuretic as a consequence of inadequate or of overdigitalization, when physically overactive, or when depleted of potassium or sodium. Such patients, when they are properly digitalized and placed at rest and their electrolyte balance is restored, usually respond promptly to diuretic therapy.

Such agents as digitalis and the xanthine derivatives, which increase renal blood flow, induce diuresis as a consequence of their cardiovascular effect, as well as of their action on the kidney. In the case of digitalis this direct renal effect is minor; in the case of the xanthine drugs, it is more pronounced.[5] In this connection it is of interest that squill has long been considered as having a specific diuretic action over and above any effect that it exerts on the circulation.[1]

The ideal diuretic is a potent, promptly acting, orally effective, nontoxic agent that accelerates the excretion of extracellular fluid without inducing any electrolyte imbalance. It also does not induce tolerance or refractoriness with continued use, as does, for example, acetazoleamide or ammonium chloride.

The available diuretics act through various mechanisms. Some increase the filtered load of sodium and chloride either by increasing the glomerular filtration rate or by increasing the concentration of the filtered ions. The most potent and widely used diuretics act by inhibiting the transport mechanisms for sodium.[12]

The use of water as a dehydrating agent was first noticed in 1690 by Sir Thomas Witherly, who was struck by the paradox of water's curing a dropsy.[5] Its effectiveness in relieving edema was emphasized by Schemm in 1942.[13] Large water loads dehydrate by inducing a negative water balance but, in excessive amounts, may also induce hyponatremia and water intoxication without diuresis or saluresis. The long practiced restriction of water in the management of edema is neither helpful nor desirable, since the retention of sodium is the primary factor responsible for the accumulation of edema.

Osmotic diuretics, which are only moderately effective and now rarely employed, depend for their action on the limited capacity of the proximal tubule for reabsorbing sodium and concentrating this ion against a high concentration gradient. In prolonged thirst and fasting, urine flow may be reduced to 150 to 450 ml./day, with a concentration four or five times that of the plasma (1200 to 1400 mOsm./l.). Osmotic diuretics inhibit reabsorption of water in the proximal tubule by the establishment of a critical gradient against which further transfer of sodium is impossible.

Salt-poor albumin, preferably, and the less expensive dextrans, gelatin, and other colloids are sometimes used for their diuretic effects, particularly in the nephroses and in cirrhosis, in which there is a reduction in the colloid osmotic pressure of the plasma. These act by increasing the colloid osmotic pressure of the plasma, thereby restraining the abnormal loss of fluid in the peripheral tissues, and by expanding the plasma volume, thereby increasing glomerular filtration and diminishing the increased production of salt-retaining hormones of the adrenal. The plasma expanders, because of their expense, potential toxicity, and difficulty of administration, have only a limited application in the nephrotic states and, occasionally, in cirrhosis, when plasma proteins are materially reduced.

Among minor diuretics of little practical importance are the cation exchange resins that remove sodium ingested in the diet. From a practical point of view, however, the obnoxiousness of ingesting large quantities of these materials outweighs the comparatively minor discomfort involved in dietary reduction of the sodium intake. Moreover, the cation exchange resins manifest an exceedingly low sodium-binding capacity in the intestine, whereas the hydrogen and ammonium resins lead to hyperchloremic metabolic acidosis and deplete the body stores of potassium.

The acidifying agents, of which ammonium chloride is most important, form hydrochloric acid in the body. The latter causes the loss of potassium and sodium ion from the cells and a gain of hydrogen ion, with a resulting decrease in the *p*H of the cell contents. Since the hydrogen bound to the intracellular buffers forms compounds that are less ionized than sodium and potassium, a reduction of the osmotic pressure within the cell results, as a consequence of which water migrates from the intracellular to the extracellular space, from which in turn it is eliminated together with sodium. The administration of the acidifying agents as well as the carbonic anhydrase inhibitors results in a compensatory increase in ammonia production, which rises and equals the acid load within three to five days. This is a consequence of an adaptive increase in glutaminase, which catalyzes the transformation of glutamine to glutamic acid and ammonia. The acidifying agents and carbonic anhydrase inhibitors thus are only effective transiently and must be used intermittently.

Theophylline, the most widely used of the xanthine derivatives, often increases the renal blood flow and glomerular filtration rate, particularly in patients without organic renal disease and in whom these functions are depressed.[14] This increase of filtration rate enhances the response to such diuretic agents as the mercurials, particularly when the glomerular filtration rate is reduced to a point at which the mercurials are no longer effective. With the availability of the newer, more potent agents this has become the most important role of the xanthine compounds as diuretics. There has been relatively little enthusiasm for the newer members of this group, such as the aminoizometridine, *sym.*-triazine, and pyrimidine compounds.

The mercurial diuretics act directly on the renal tubules, blocking the reabsorption of sodium and chloride ions, which results in an increased urine flow and elimination of salt. There is still some question regarding their exact mode of action and whether they act entirely on the sodium or the chloride ion.[14] They exert their main inhibitory effects on ion transport in the proximal tubule and are themselves actively secreted in this same segment.[15]

By far the most important of the available diuretics are the recently introduced benzothiadiazine derivatives,[16,17] which are discussed in detail elsewhere in this monograph and therefore need be referred to only briefly here. The superiority of this group of diuretics, as regards effectiveness, ease of administration, and relative lack of undesirable side effects, has made them the drugs of choice and will undoubtedly render most of the older diuretics obsolete. The introduction of this series of compounds has also extended the use of diuretics to the management of hypertension, a field of application more extensive than the prior use of these drugs in the relief of edema.

Although the claim has been made that the benzothiadiazine derivatives exert their hypotensive action by mechanisms other than those concerned in the elimination of sodium, it is probable that these play only a minor role, since equally striking effects may be elicited in the human as well as in the experimental animal by drastic sodium restriction.[18] With the administration of large doses of these drugs, more effective sodium depletion is obtained than by dietary restriction. This depletion of sodium, combined with the effects of potassium loss and perhaps other deleterious effects, may induce a more striking hypotensive action than is observed with sodium restriction alone.

The most recent additions to our diuretic armamentarium are the aldosterone antagonists. In view of the important role of the adrenal hormones in water and electrolyte metabolism as well as their effects on vascular integrity and permeability it would be anticipated that they and their antagonists might be useful in disease. This has proven to be the case, although the exact indications for their use are not established.

The effectiveness of large doses of the glucocorticoids in nephrosis secondary to collagen disorders is well established. Here, presumably, the effect of these agents in inhibiting the primary disturbance in the glomeruli overbalances the tendency of large doses of these drugs to induce salt and water retention. The effect of the glucocorticoids in establishing vascular integrity also may explain their action in relieving edema in other disorders.

Of more recent interest as diuretics are compounds that inhibit the action of aldosterone on the kidney. These exert their diuretic effect by antagonizing the action of aldosterone, which not only is responsible for the normal retention of salt and water by the kidney but may be produced in excessive amounts in certain edematous states. Although sometimes effective, the aldosterone antagonists often fail to exert their anticipated action, since the adrenal compensates by secreting other sodium-retaining hormones, such as desoxycorticosterone.[3] Under these conditions the simultaneous administration of a glucocorticoid for suppressing adrenal cortical activity has proven effective.

Conclusion

The use of diuretics has assumed an increasing importance in therapeutics, particularly as a result of the introduction of the newer orally effective benzothiadiazine derivatives in the management of hypertension. The most recently introduced members of this group approach the ideal of diuretic therapy, being relatively nontoxic, highly potent, and effective when administered orally. The introduction of compounds effective in overcoming the effects of the normal hormonal factors responsible for the retention of sodium promises an additional approach to diuretic therapy.

Despite the notable advances in diuretic therapy, one should not lose sight of the fact that edema and sodium retention are in most cases a consequence of extrarenal disturbances, to which the kidney responds only secondarily. Attention, accordingly, must always be directed to improving the function of the heart or otherwise affecting the primary disturbance, rather than to relying solely on the use of diuretics, the action of which, in most cases, is only symptomatic.

Although reference is often made to the "ideal" diuretic, it is obvious that such interference with renal function as is necessary for inducing diuresis will be accompanied by alterations in such related renal functions as disturbed electrolyte and acid-base balance, hormonal disturbances activated to maintain homeostasis, and interference with the excretion of uric acid and other catabolites. These undesired reactions as well as other untoward effects must always be anticipated and counteracted when possible by supplementary measures.

Optimal and effective diuretic therapy requires an understanding of the nature of the basic disturbance before a selection may be made, from the available measures, of those that best counter the underlying pathological process.

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ANIMAL PHARMACOLOGY OF THE NEW DIURETICS: BENZOTHIADIAZINES, SPIROLACTONES, AND PHTHALIMIDINES

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The newer nonmercurial, orally effective diuretics may be divided into three chemical groups: the benzothiadiazines, the antialdosterone spirolactones, and the phthalimidines. This presentation of the pharmacological studies will be similarly divided.

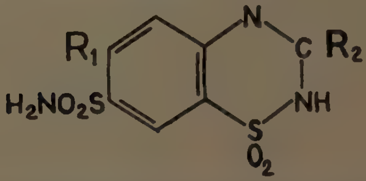
Benzothiadiazines

The history of the search for the benzothiadiazines gives some insight into the mechanism of diuretic action that they exhibit. Sulfonamyl compounds, the early example being sulfanilamide, were found to have diuretic activity. They were found to have a specific action in blocking carbonic anhydrase. Blockade of this enzyme decreases availability of hydrogen ion and hence decreases tubular reabsorption of sodium and bicarbonate. This results in increased excretion of sodium and bicarbonate, and the urine *p*H increases. Potassium excretion is also enhanced. On a long-term basis, therapy with carbonic anhydrase inhibitors results in potassium loss from the body and disturbances of acid-base balance. In the search for safer and more effective diuretics, Novello and Sprague[1] developed a compound that combined a thiadiazine ring and a benzene ring, which had a sulfamyl substitution at 7 and a chlorine substitution at 6. Beyer[2] found that this compound, chlorothiazide, introduced a new property, the ability to block sodium chloride reabsorption by the renal tubule. The resultant diuretic effect is predominantly a natriuresis and chloruresis. These compounds act as though they were impairing the sodium pump in the proximal cells, thereby preventing the reabsorption of large quantities of sodium. This action on the sodium pump is most selective in the more potent derivatives, and very little carbonic anhydrase inhibitory activity remains. This action on sodium and chloride is referred to as a mercurylike action, and in dogs it is capable of inhibiting about 10 per cent of the energy supply to the pump. Later I shall refer to this mercurylike action in more detail.

Table 1 presents the chemical configurations of each of the benzothiadiazine compounds, their generic names, and trade names. The compounds are arranged roughly in the order of their natriuretic and chloruretic potency. One outstanding feature seems to be the extreme change in activity with minor structural change involving R_1, R_2, or both. The initial effective benzothiadiazine was chlorothiazide. This possessed 6 chloro-7 sulfamyl substitutions on the benzene nucleus. There is an unsaturated bond at the 3-4 position. The simple addition of hydrogen at R_2 to reduce this double bond produced hydrochlorothiazide, and the natriuretic potency increased about 10-fold. The carbonic anhydrase inhibitory activity decreased about 10-fold. The substitution of a trifluoromethyl group at the 6-position gave an equipotent compound with less carbonic anhydrase inhibitory activity.* If at R_2 a benzyl substitution is made, further increase in natriuretic potency ensues that is five to ten times that of the 6-trifluoromethyl derivative. So too with the dichloromethyl substitution at R_2. These structures with unique selectivity and extreme potency offer a means for the study of sodium transport mechanisms and the action of mercurials.

TABLE 1

BENZOTHIADIAZINE DIURETICS



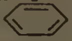
Generic name	Trade name	Company	R_1	R_2
Chlorothiazide	Diuril	Merck	Cl	H
Flumethiazide	Ademol	Squibb	CF_3	H
Hydrochlorothiazide	Hydrodiuril	Merck	Cl	H_2
	Esidrix	Ciba	Cl	H_2
	Oretic	Abbott	Cl	H_2
Hydroflumethiazide	Hydro Ademol	Squibb	CF_3	H_2
	Saluron	Bristol	CF_3	H_2
Trichloromethiazide	Naqua	Schering	Cl	H—$ChCl_2$
Benzydroflumethiazide	Naturetin	Squibb	CF_3	H—CH_2 

TABLE 2

RELATIVE POTENCIES OF BENZOTHIADIAZINES AS CARBONIC ANHYDRASE INHIBITORS AND AS NATRIURETIC AGENTS

	Carbonic anhydrase inhibition	Natriuretic activity
Sulfanilamide	1	
Acetazolamide	200	
Chlorothiazide	10	1
Hydrochlorothiazide	0.7	13
Flumethiazide	0.5	1
Dihydroflumethiazide	0.1	13
Benzydroflumethiazide	0.1	40
Trichlormethiazide	0.3	50

TABLE 2 shows the relative activities of these compounds in respect to natriuretic activity in rats and to carbonic anhydrase inhibition *in vitro*. These values are but approximate, for it was necessary to interpret quantitative results in animal studies from many different sources. It is in general clear, however, that there is a decreasing order of carbonic anhydrase inhibitory potency with increasing natriuretic potency. The chloruretic potency is in the same range as the natriuretic potency. Excretion studies in dogs have revealed that carbonic anhydrase inhibition is nearly absent with effective diuretic doses of the more potent benzothiadiazines. The urine remains acid, and only a slight increase in K excretion results. These compounds are surprisingly nontoxic. In mice, rats, and dogs several grams per kilogram given orally were without acute effect, and large doses administered daily for several months to dogs resulted in no evidences of toxicity.

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* A benzylthiomethyl group in position 3 results in a 10-fold increase over chlorothiazide. Benzthiazide is the generic name for this compound, developed by Chas. Pfizer & Co., Inc., Brooklyn, N.Y.

The oral effectiveness of all of these benzothiadiazines has been a clinical advantage. Nearly complete and rapid absorption occurs from the alimentary canal. Large quantities are excreted in bile.

In animal studies a striking absence of other pharmacological effects was found. The interested laboratories have subjected the drugs to tests for the well-recognized types of pharmacodynamic action. No definite activity on other organ systems has been described.

TABLE 3
RENAL CLEARANCE RATIOS OF BENZOTHIADIAZINES

	Drug clearance (glomerular filtration rate)
Chlorothiazide	3.0
Hydrochlorothiazide	4.0
Flumethiazide	3.5
Dihydroflumethiazide	1.6
Benzydroflumethiazide	0.7
Trichlormethiazide	1.0

I shall return now to a discussion of the renal effects of these benzothiadiazines and their renal excretion patterns. Also I shall compare and contrast them with the organomercurials. These benzothiadiazine compounds are excreted by renal tubular excretion as well as by glomerular filtration. Plasma protein binding occurs to a large extent with the compounds studied. The rate of tubular excretion is very great in some cases and may be four times greater than the glomerular filtration rate measured by creatinine clearance in the dog.[3,4]

The rate of net renal tubular excretion varies from one analogue to another and seems to bear an inverse relation to the natriuretic and chloruretic activity (TABLE 3).

Baer *et al.*[5] showed that the excretion of these compounds is inhibited by probenecid. Thus these compounds presumably are excreted by the same renal tubular transport mechanism that secretes para-aminohippurate (PAH), Diodrast, phenol red, and penicillin.

Stop-flow experiments (Vander *et al.*[6] and Kessler *et al.*[7]) have shown that the site of tubular excretion of chlorothiazide is the proximal tubule. These stop-flow experiments also localize the site of action of benzothiadiazines on the sodium transport. The predominant effect is on the proximal tubule, thus preventing sodium reabsorption.

Although the diuretic response to benzothiadiazines and organomercurials is similar at neutral *p*H of the urine, the similarity ends with the changes in urinary *p*H. If the urine be made strongly alkaline the mercurial diuretics lose their effectiveness. The benzothiadiazines retain their effectiveness in alkaline and acidic urines.[5] Carbonic anhydrase inhibitors lose their potency in a strongly acid urine. Furthermore, BAL blocks the action of mercurial diuretics, whereas it has no effect on chlorothiazide.

To bring this discussion full circle I should like to refer to experiments on mercurial diuretics that may suggest a unifying aspect of organic mercurial action and the mercurylike action of the sulfonamyl benzothiadiazines. Organomercurials have been shown to be excreted by the renal tubule,[8] as are the benzothiadiazines. Campbell[9] of Uppsala, Sweden, has been studying the mechanism of organomercurial diuresis and its relation to the tubular excretion of the organomercurial, using the renal portal circulation to the kidney in the hen. This technique allows the direct administration of substances to the renal tubular cells of one kidney, while the other kidney acts as its control. Urine is collected separately from each kidney. Unilateral administration of organomercurials produced an excess excretion of the mercurial ipsilaterally, accompanied by an ipsilateral diuresis. Campbell found that previous administration of probenecid prevented the excess ipsilateral renal tubular secretion of the organomercurial. Probenecid, when administered before the organomercurial, also prevented the ipsilateral diuresis that otherwise would have occurred. If, however, Campbell gave the mercurial and then, within 2 minutes, gave probenecid, the diuresis was tremendously increased (FIGURE 1). One of Campbell's interpretations is that probenecid, when given before

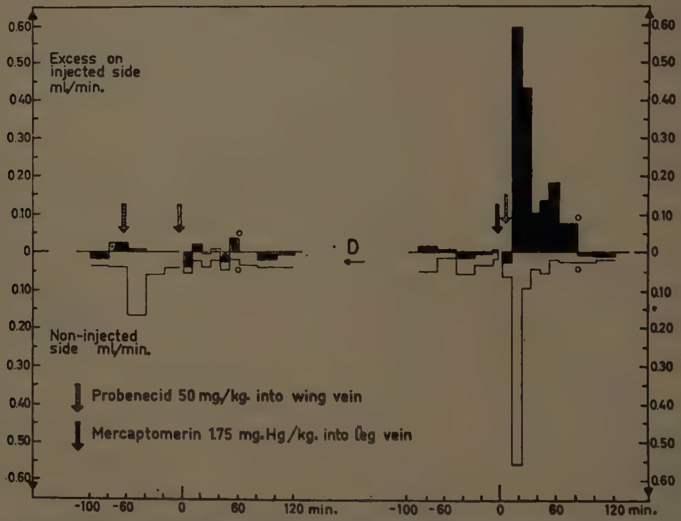

FIGURE 1. *Left*, inhibition of water diuresis due to mercaptomerin by preinjection of probenecid. *Right*, potentiation of water diuresis due to mercaptomerin as a result of subsequent probenecid (Campbell[9]).

mercury, blocks the entry of the organomercurial into the tubular cell and hence prevents its ipsilateral tubular secretion and ipsilateral diuretic effect. However, once the organomercurial has gained entry into the cell, it may have its action potentiated, because probenecid administered after the mercurial can prevent its excretion from the cell into the lumen. I present these observations because they make an attractive analogy to the transport of the benzothiadiazines by the probenecid-sensitive system and suggest the possible identity of organomercurial tubular transport and that of the benzothiadiazines. Furthermore, they suggest a relation between transport and diuretic action in the case of the organomercurials. Mercurials do affect the PAH transport in humans and not in dogs, so that species differences may prove a difficult hurdle in further study.

Pitts *et al.*[10] have studied the interrelationship of the benzothiadiazines and organomercurials in dogs. He found that the effects of chlorothiazide and chloromerodrin were additive. He suggested that these two substances block different mechanisms or interfere with different enzymatic reactions supplying energy to a common mechanism for sodium transport.

In collecting the experimental evidence from different species one can speculate about the fact that probenecid can block the tubular transport of both organomercurials and benzothiadiazines. At the same time probenecid can block the diuretic effect of the organomercurial or can potentiate it, depending on the sequence of administration.

Antialdosterone Compounds

The discovery of aldosterone and its possible role in diseased states promoted interest in compounds that could antagonize aldosterone. A group of agents that can antagonize the effects of aldosterone has been developed.* These compounds seem to act by competitively inhibiting the effects of aldosterone.

These steroidal 17-spirolactones contain a five-membered lactone ring attached to the C_{17} position of the steroid nucleus. This structure is not unlike the hemiacetal form of aldosterone. The structure of major clinical importance (FIGURE 2) is the C_7 acetyl-thio derivative, which has oral activity equal to parenteral activity. The compound has the trade name of Aldactone (SC 9420); the generic name is spirolactone. Two other derivatives may be referred to by number, SC 5233 and SC 8109. The last compounds lack oral activity and have been investigated chiefly in animals.

Kagawa *et al.*[11] showed that these spirolactones acted on the renal excretion of sodium and potassium to antagonize the effects of desoxycorticosterone acetate (DCA) or aldosterone. In rats 24 hours after adrenalectomy spirolactones were without effect on the excretion of sodium and potassium. When these adrenalectomized rats were treated with aldosterone, they developed a low sodium:potassium ratio in the urine. When during a standard aldosterone test spirolactones were administered to these adrenalectomized rats, the urinary ratio of sodium to potassium rose, and there was a smooth dose-response relationship, indicating the competitive nature of the antagonism. This same experiment may be repeated with DCA in place of aldosterone, since the blocking effect of the spirolactones is in the same direction. SC 9420 proved as effective orally as subcutaneously. Similar antagonistic effects were demonstrable after treatment with hydrocortisone.

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* By the Research Department of G. D. Searle & Co., Chicago, Ill.

The two analogues of spirolactone have been used in animal experiments. SC 5233 and SC 8109 showed no effect on electrolyte excretion in adrenalectomized dogs, yet they competed with administered aldosterone.[12] SC 5233 in rats showed no effect after adrenalectomy on electrolyte excretion. However, it competed with administered aldosterone, as did SC 9420 (FIGURE 3). An additional antihypertensive action of SC 5233 was demonstrated in rats by Sturtevant.[13] When rats were treated with DCA and given salt they developed a rise in blood pressure that could be prevented or reversed by the simultaneous administration of SC 5233. Another mechanism for producing hypertension in rats is treatment with DCA to produce hypertension (FIGURE 4); after the removal of administered DCA a hypertension persists. This so-called metacorticoid hypertension was produced in rats, and treatment with SC 5233 was begun. Sturtevant found that SC 5233 caused a decrease in the metacorticoid hypertension whether given acutely or chronically. The hypertension that occurs during adrenal regeneration in rats was prevented by chronic administration of SC 5233.[14]

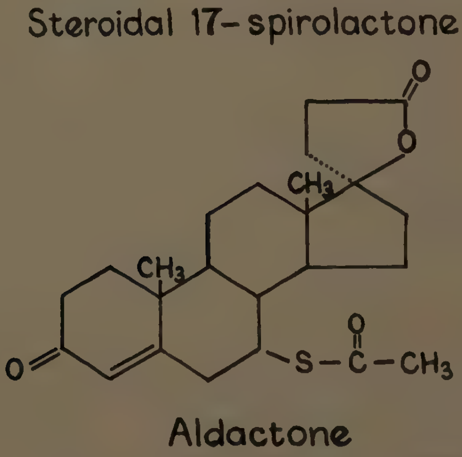


FIGURE 2. Structure of spirolactone (SC 9420).

There are no detectable pharmacological effects of these compounds when they are surveyed by the usual laboratory methods except for a progesterone-like activity of SC 5233 and SC 8109. Spirolactone (SC 9420) had no measurable progesteronelike activity.

The action of these compounds on renal electrolyte excretion results in sodium excretion and potassium retention. This places them in a separate group, since most diuretic agents increase sodium excretion and simultaneously increase potassium excretion to varying degrees.

A recent report of Sayers *et al.*[15] indicated an interesting physiological effect of aldosterone in rats. Sayers and his co-workers found a striking increase in the functional capacity of the perfused heart when aldosterone was administered. This might make an interesting *in vitro* test object on which to assay antialdosterone activity.

In summary, it seems from animal tests that the action of the spirolactones is to inhibit competitively the effects of DCA and aldosterone on electrolyte

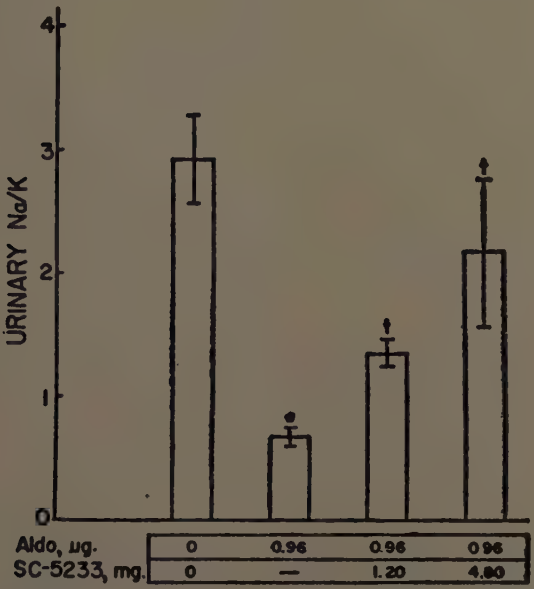


FIGURE 3. Effects of SC 5233 in blocking urinary Na/K action of aldosterone in adrenalectomized rats (Kagawa *et al.*[11]).

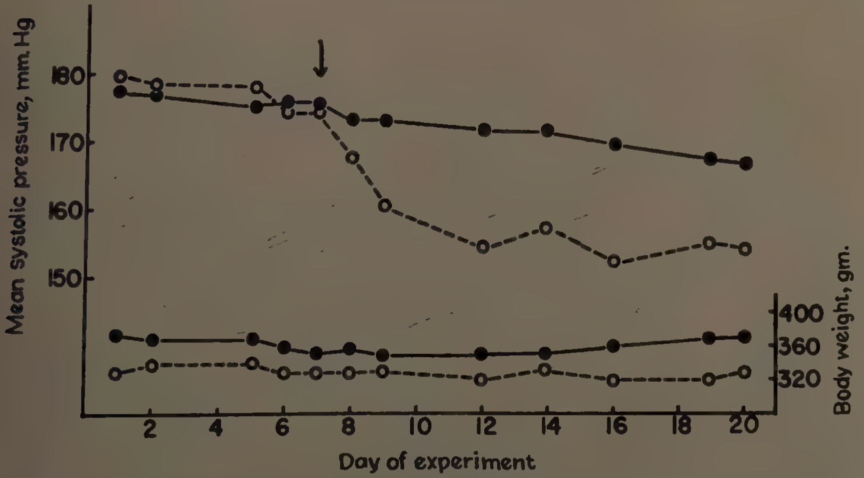


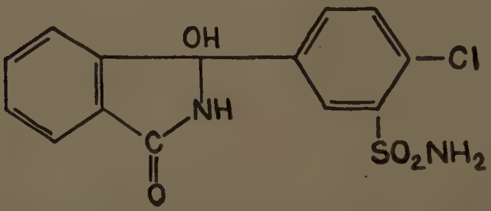
FIGURE 4. Effects of SC 5233 on blood pressure and body weight in metacorticoid hypertensive rats. Solid dots, controls; open circles, treated. Arrow represents beginning of daily treatment with 20 mg./kg. SC 5233.

excretion in the kidney. The spirolactone had no action in adrenalectomized rats or dogs unless DCA or aldosterone were administered. The dose response relationships indicate that the inhibition of DCA or aldosterone is on a competitive basis.

Phthalimidines

At the J. R. Geigy Company a series of sulfonamyl benzophenone derivatives has been investigated by Stenger *et al.*[16,17] for diuretic activity. The most useful member is 1-oxy-3-(3′-sulfamoyl-4′-chlor-phenyl)-3-hydroxy-isoindolin with the trade name Hygroton (FIGURE 5). In unanesthetized dogs 5 mg./kg. of Hygroton by mouth increased sodium excretion from 15 μEq./min. to 103 μEq./min., potassium excretion doubled to 30 μEq./min., and chloride excretion increased to 20 times. Hygroton 0.5 mg./kg. gave one half the response of 5 mg. After 13 to 14 hours the effect of a single dose was still apparent. The carbonic anhydrase inhibitory activity was 17 times as great as that of sulfanilamide by *in vitro* assay. The acute LD_{50} after oral administration exceeded 5 gm./kg. in rats and mice.

Phthalimidine compound



Sulfamylated benzophenone
Hygroton

FIGURE 5. Structure of phthalimidine.

Chronic oral administration to dogs led to only moderate changes in serum electrolytes and no signs of hypopotassemia.

Hygroton produced its usual diuretic effects in both acidosis and alkalosis. Hygroton produced no pronounced pharmacological effects and did not alter renal clearance of PAH or creatinine.[18] The dog excretes it rapidly. In rabbits, tissue distribution studies revealed the highest levels in the kidney.

Antidiuretic Actions of the Newer Diuretics

Kennedy and Crawford[19] have made interesting observations on the antidiuretic effect of the benzothiadiazines and phthalimidines in diabetes insipidus produced experimentally in rats. They conclude that the mechanism of action is an antimineralocorticoid effect. They found that probenecid, which interferes with the tubular secretion of chlorothiazide, did not reduce its antidiuretic activity. Carbonic anhydrase inhibitors such as acetazolamide did not cause antidiuresis.

It is concluded that neither the route of tubular secretion nor the carbonic anhydrase inhibitory action of chlorothiazide caused its antidiuretic affect. Recent experimental results in Kennedy's laboratory suggest that the antidiuresis produced by chlorothiazide and similar drugs depends partly upon blocking the action at the kidney of the mineralocorticoid hormone of the adrenal cortex.

The evidence of inhibition of mineralocorticoid action on the kidney is as follows:

(1) In rats with experimental diabetes insipidus the reduction of urine output that followed maximally effective doses of hydrochlorothiazide was duplicated by adrenalectomy. After adrenalectomy no further antidiuretic action could be induced by the drug. Hydrochlorothiazide had no saluretic action in adrenalectomized rats.

(2) Little expansion of the urinary output of the adrenalectomized rat with diabetes insipidus followed daily injection of cortisone, but polyuria could be restored by giving desoxycorticosterone. This action of desoxycorticosterone was completely blocked by hydrochlorothiazide.

(3) The daily injection of desoxycorticosterone into rats with diabetes insipidus doubled the urinary volume. No increase in volume occurred when hydrochlorothiazide was given at the same time.

(4) Prolonged treatment of normal rats with desoxycorticosterone caused a condition like diabetes insipidus. This form of polyuria was decreased by hydrochlorothiazide.

(5) Two antialdosterone compounds, SC 8019 and SC 9420, were antidiuretic in experimental diabetes insipidus. Their antidiuretic effect was antagonized by desoxycorticosterone.

Further studies of water and electrolyte balance and glomerular filtration rate should help to elucidate this mechanism.

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HUMAN CLINICAL PHARMACOLOGY OF THE NEWER DIURETICS: BENZOTHIADIAZINE AND PHTHALIMIDINE

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Benzothiadiazines

The introduction of chlorothiazide several years ago[1] stimulated active research in the benzothiadiazine group of diuretic agents. As a result of this research there has emerged a group of potent diuretics that have characteristics common to the thiazide group but there are pharmacological differences among these drugs that result from seemingly very minor changes in the basic benzothiadiazine structure.

In FIGURE 1 the structural formula of the thiazide diuretics is shown. The changes that have been made in chlorothiazide, the parent compound, are at the third, fourth, and sixth positions. The pharmacology of these diuretics can be divided into three groups at this stage of their development.

Nonhydrogenated thiazide. The nonhydrogenated thiazides in clinical use today are chlorothiazide* (Diuril) and flumethiazide† (Ademol), FIGURE 1. These agents have an effective dose range of 200 mg. to 2000 mg. Doses greater than 2000 mg. give no greater saluretic or diuretic effects than the 2000 mg. dose itself. They have significant effects on the electrolyte excretion in the urine, with major influence on the sodium, potassium, and chloride ions. The quantity of sodium and chloride excreted is approximately the same. Potassium excretion with chlorothiazide increases with dosage of the drug and is greatest at the maximum doses, where the carbonic anhydrase inhibiting activity is most evident. With the substitution of the chloride atom by a trifluoromethyl group at the sixth position of chlorothiazide, which results in flumethiazide, there appears to be a change in the effect on potassium excretion. There is an increase in potassium excretion doses up to 400 mg. but, unlike chlorothiazide, larger doses do not appear to have any greater influence.[2]

Hydrogenated thiazides. By the addition of two hydrogen atoms at the third and fourth positions of the basic structure the hydrogenated group of thiazides is produced. The hydrogenation of chlorothiazide results in hydrochlorothiazide‡ (Hydrodiuril, Esidrix, Oretic), and the addition of the hydrogen atoms to the third and fourth positions of flumethiazide results in hydroflumethiazide§ (Saluron), FIGURE 1.

The hydrogenation of these compounds reduces their dose range to 25 to 200 mg., and doses greater than 200 mg. have no greater effect on sodium excretion. Thus a dosage ratio of 10:1 exists between the nonhydrogenated and hydrogenated drugs mentioned.[3] Another pharmacological characteristic of hydrogenation is the change in the electrolyte excretion pattern. The

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* Supplied by Merck Sharp & Dohme, West Point, Pa.

† Supplied by E. R. Squibb & Sons, New York, N.Y.

‡ Hydrochlorothiazide, supplied by Merck Sharp & Dohme, West Point, Pa. (Hydrodiuril); Ciba Pharmaceutical Products, Inc., Summit, N.J. (Esidrix); and Abbott Laboratories, Inc., North Chicago, Ill. (Oretic).

§ Hydroflumethiazide, supplied by Bristol Laboratories, Syracuse, N.Y.

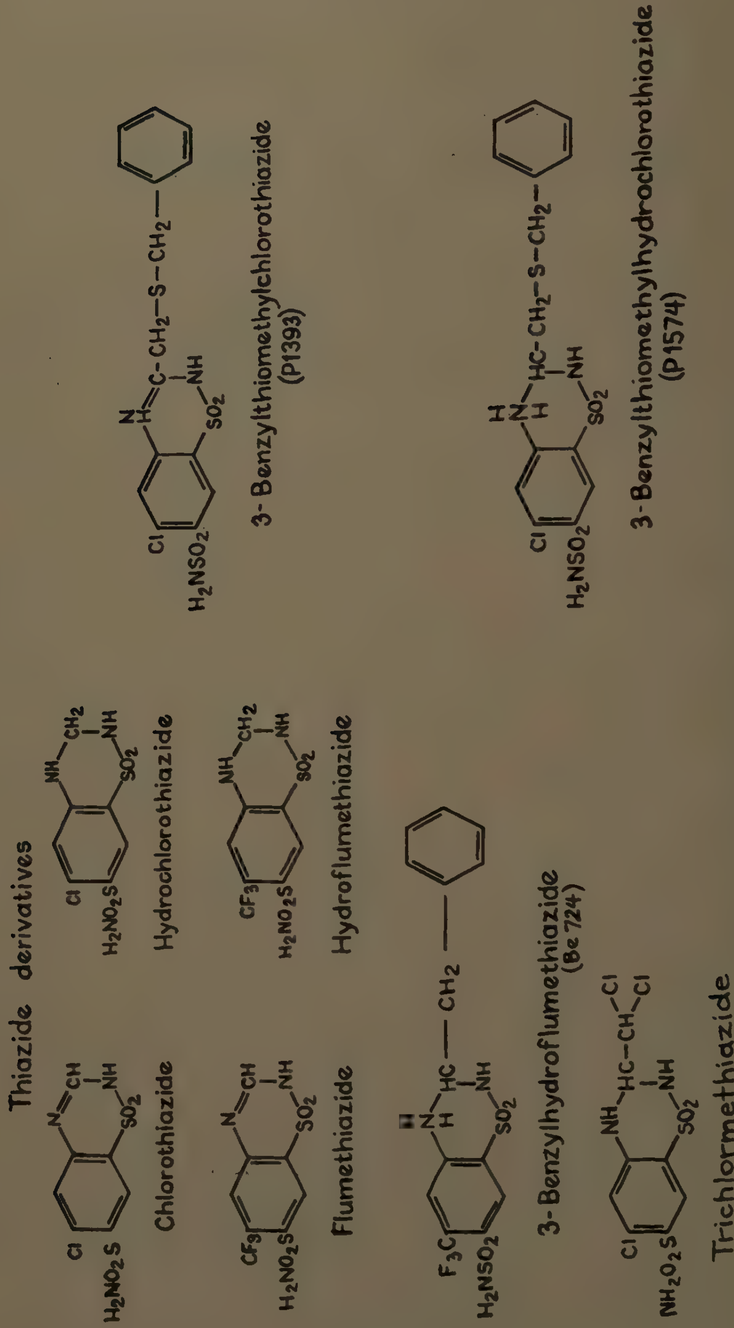
Thiazide derivatives
Chlorothiazide
Hydrochlorothiazide
Flumethiazide
Hydroflumethiazide
3-Benzylhydroflumethiazide (Be 724)
Trichlormethiazide
3-Benzylthiomethylchlorothiazide (P1393)
3-Benzylthiomethylhydrochlorothiazide (P1574)

FIGURE 1. Structural formulas of the benzothiazine diuretics.

chloruretic activity exceeds the natriuretic activity so that urinary chloride is frequently greater than sodium excretion (FIGURE 2).

3-Hydrogenated thiazides. A further change in the pharmacological characteristics of the thiazide group of diuretics has been made by the addition of a benzyl group at the third position of hydroflumethiazide, resulting in benzflumethiazide,* (Naturetin); and by the addition of a dichloromethyl group at the third position of hydrochlorothiazide which results in trichlormethiazide† (Naqua). These drugs form the third group of the thiazides, the 3-hydrogenated structures. As a result of these additions, a further reduction in the dose ranges is made so that now the effective dosage range with these two agents is between 1 mg. and 10 mg., and doses greater than 10 mg. have no greater effects on sodium excretion. These drugs, with markedly reduced dose ranges and marked increase in potency by milligram weight, appear to produce less potassium excretion with acute administration and therefore have a favorable sodium:potassium excretion ratio in the urine.[4]

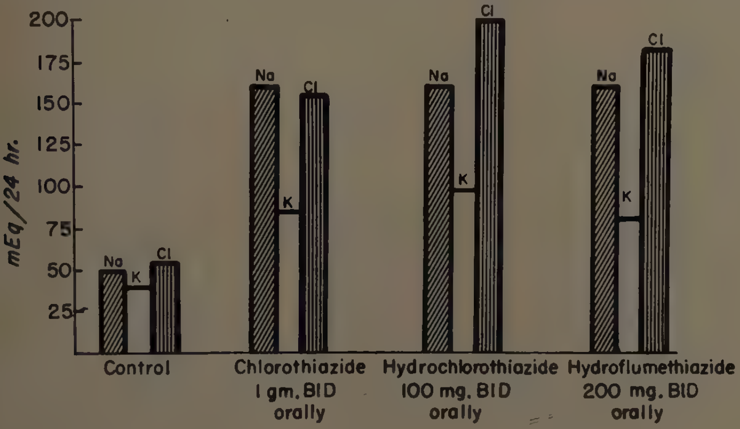

FIGURE 2. The urinary electrolyte excretion pattern of chlorothiazide (nonhydrogenated thiazide) and hydrochlorothiazide (hydrogenated thiazide). The chloride excretion is significantly greater with the hydrogenated compounds.

General considerations. The administration of the thiazide diuretics results in prompt natriuresis and diuresis, and the duration of activity may extend from 12 to 24 hours (FIGURE 3). These drugs are of great value due to their marked potency and ease of administration by the oral route. Fortunately, toxicity has been insignificant, although occasional gastrointestinal complaints or skin rashes with or without thrombocytopenia have been noted.[5,6]

The action of the thiazide group of diuretics depends upon their ability to block enzyme systems at the proximal and distal renal tubules. These drugs do not have significant effects on glomerular filtration rate or renal plasma flow (FIGURE 4).

The thiazides also have value in their ability to promote continuous diuretic and natriuretic activity and do not develop a refractory period after several days of administration, as may be seen with the carbonic anhydrase inhibitors. In FIGURE 5 the continuous excretion of sodium above control levels is demonstrated in a congestive heart failure patient given daily thiazide therapy. The sodium and water excretion do not fall to control levels until the patient has attained cardiac compensation and is free of excess sodium stores and edema fluid.

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* Benzflumethiazide, supplied by E. R. Squibb & Sons, New York, N.Y.

† Trichlormethiazide, supplied by Schering Corporation, Bloomfield, N.J.

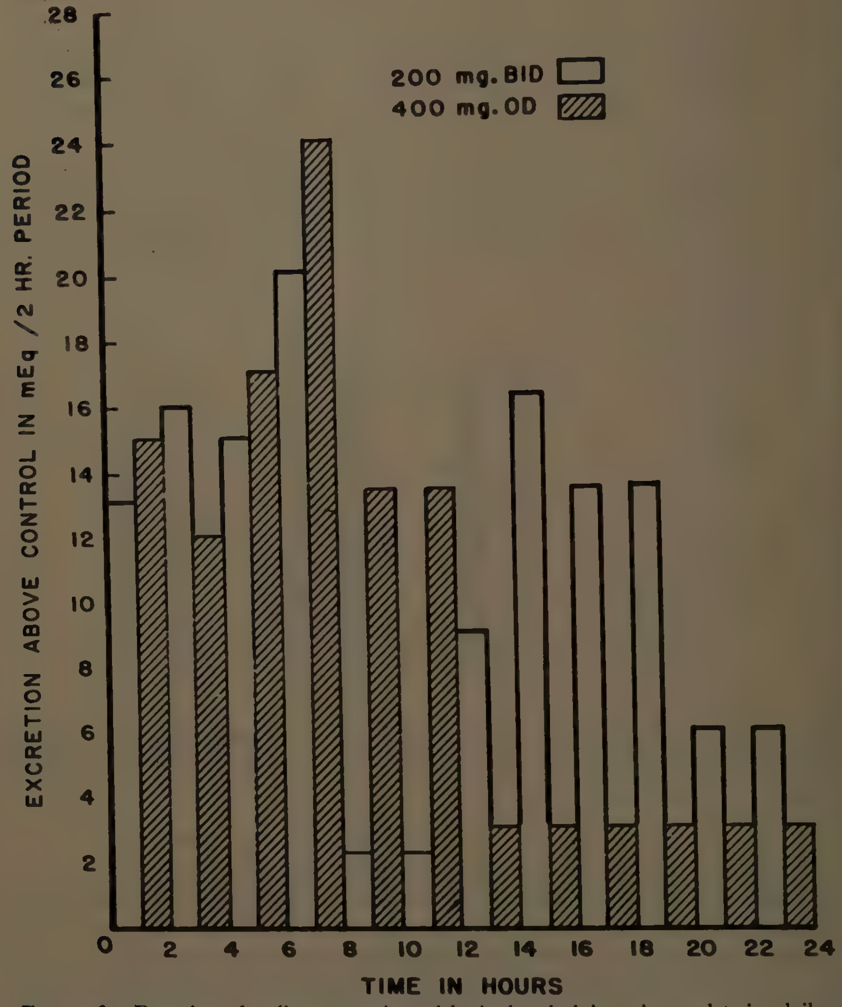


FIGURE 3. Duration of sodium excretion with single administration and twice-daily administration of hydrochlorothiazide. Reproduced by permission from the *A. M. A. Archives of Internal Medicine.*[3]

The responsiveness to the thiazide diuretics has been, in general, quite gratifying in most edema syndromes. The degree of response and the comparative efficacy of diuretics are difficult to determine, since the diuretic and natriuretic response is not only dependent upon the pharmacologic characteristics of the drug but also upon the responsiveness of the patient. The dynamic state of the pathophysiological influences that play upon the renal tubules will significantly influence the diuretic response to a drug. This continuous change in the patient's response as a result of the dynamics of pathophysiology creates a difficulty in comparing the efficacy of diuretics.

When the sodium excretion of the three groups of thiazide diuretics are compared in patients that are free of edema and on metabolically controlled sodium and fluid balance, we find that the maximum effective dose of each group of the thiazides influences sodium excretion similarly. The dose ranges by milligram weight may vary from a 200:1 ratio, but the over-all diuretic and natriuretic efficacy is the same for the three groups (FIGURE 6). This is also borne out by the clinical application of the drugs.

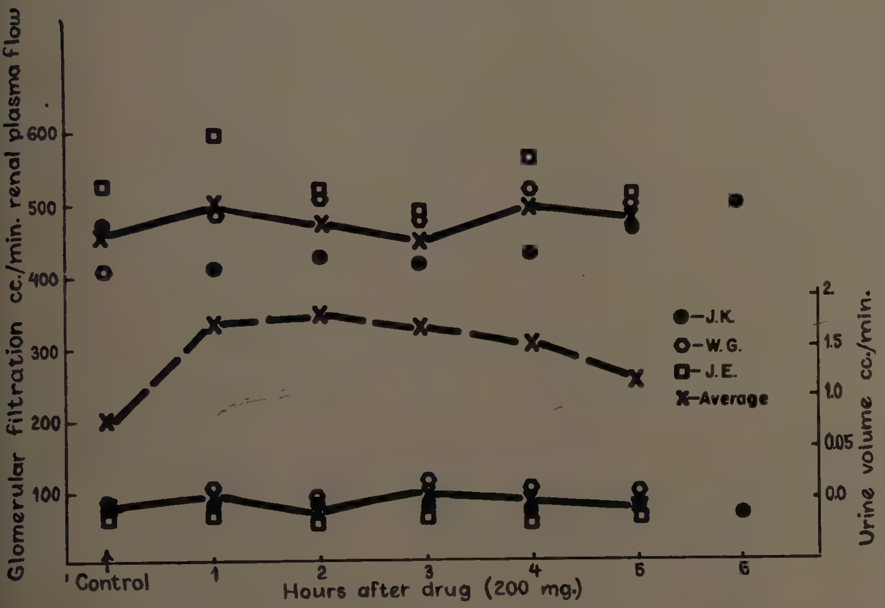


FIGURE 4. The effect of oral hydroflumethiazide on renal function and urine volume. The thiazides have no significant effect on renal plasma flow or glomerular filtration rate, but produce a prompt diuresis within one hour of oral administration. Reproduced by permission from *Geriatrics*. **15:** 373 (1960).

The problem of tolerance with the chronic use of the benzothiadiazine diuretics is still to be evaluated. It is our impression that tolerance does occur occasionally, but poor response to the drug due to progression of the disease process or change in the dynamics or severity of the physiopathology may be misconstrued as tolerance. Occasionally, one thiazide does not have the desired effectiveness while another of the benzothiadiazine group may produce a good response. The diuretic effects of the thiazides are not as great as those

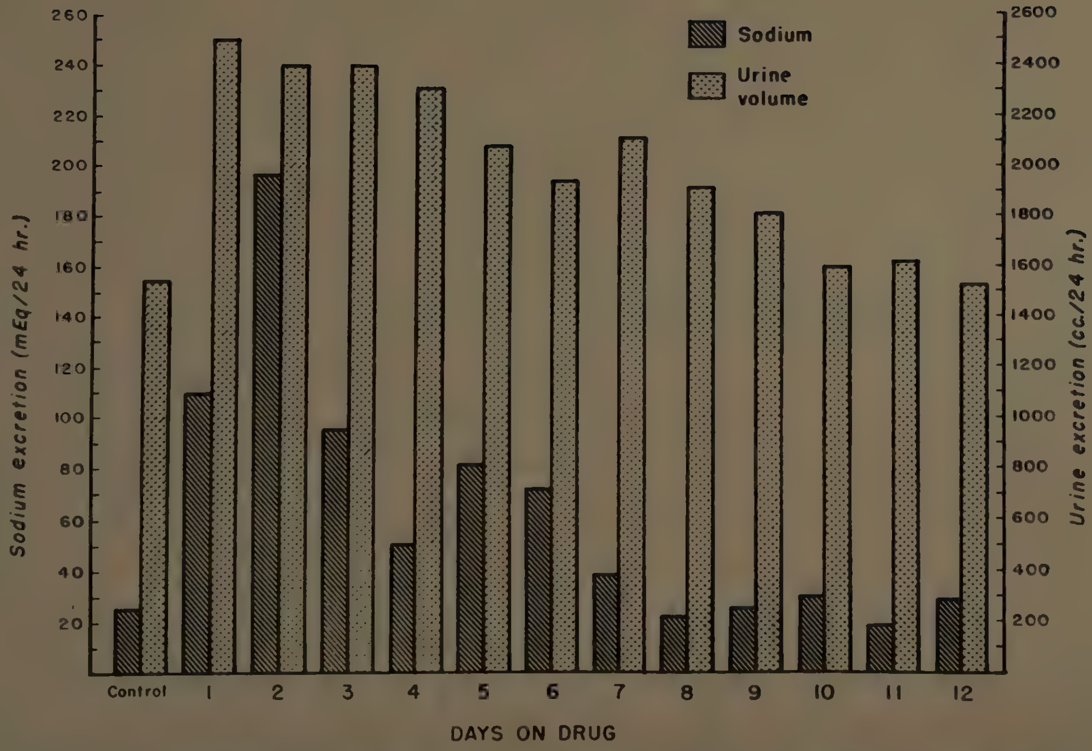


FIGURE 5. Hydroflumethiazide (100 mg., twice daily) response during loss of edema fluid. Sodium and water excretion in a heart failure patient given daily thiazide therapy. Reproduced by permission from *Geriatrics*. **15:** 373 (1960).

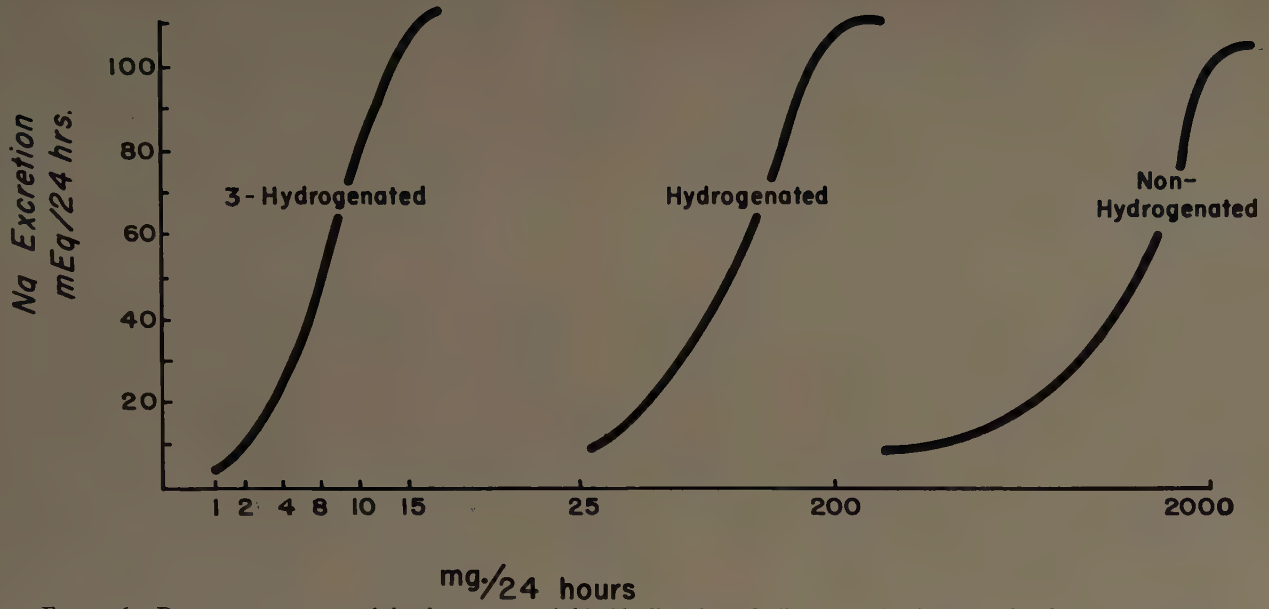
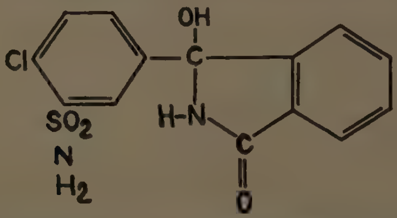


FIGURE 6. Dose response curves of the three groups of thiazide diuretics. Sodium excretion is similar for the maximum effective dose of each group.

of the parenteral mercurials, which still remain the most effective diuretic agents available. The combined use of both mercurials and thiazides may have an additive and beneficial effect in the patient with poor response to each of the drugs alone.

The long-term use of the thiazide derivatives may produce electrolyte imbalances. The possibility of hypokalemia must be considered with chronic use of any benzothiadiazine, regardless of the effect on potassium excretion with acute administration, since the long-term effect of any potent diuretic agent may produce hypokalemia as well as hyponatremia and hypochloremia. Hypochloremic alkalosis is not an uncommon metabolic imbalance with these drugs, and should be suspected when response to the drugs decreases or the patient's clinical course deteriorates. The elevation of blood urea nitrogen with chronic use of the thiazides may occur, due to sodium depletion and a decrease in circulating plasma volume. Administration of these agents to patients with renal insufficiency should be undertaken cautiously. The ability of the thiazides to elevate blood uric acid levels is well known, and the possibility of precipitating a gouty attack in the susceptible individual should be considered and avoided if possible.



3-hydroxy-3-(4-chloro-3-sulfumylphenyl) phthalamidine
(G 33182)

FIGURE 7. Structural formulas of the phthalimidine diuretic. Note similarity of some of this structure to that of chlorothiazide.

Phthalimidines

The advances made in diuretic research in recent years have been quite significant, as demonstrated by the clinical efficacy of the benzothiadiazine group of diuretics. Since none of the available diuretic agents in clinical use today has provided the necessary diuretic effects in all edema problems, further evaluation of newer groups of agents is still actively pursued. The most recent addition to our clinical diuretic armamentarium is the phthalimidine group of diuretic agents, of which 3-hydroxy-3-(4-chloro-3-sulfamylphenyl) phthalimidine* (Hygroton) has received significant clinical evaluation (FIGURE 7). In a previous preliminary report[7] the acute 48-hour weight response and chronic administration of the phthalimidine derivatives in congestive heart failure patients were described.

The 48-hour weight loss following administration of increasing doses of this drug to a group of congestive heart failure patients is shown in FIGURE 8. In this particular study a significant weight loss with the phthalimidine drug was achieved with the 200- and 400-mg. doses. Doses greater than 400 mg. had no further significant effects on weight loss with acute administration in this group of patients. The reason for the absence of significant weight response with the 50- and 100-mg. doses in this group of patients is not apparent, but a general survey of dose range is determined by this method. It should be added that the 48-hour significant weight response was also accompanied by an improvement in the congestive heart failure symptoms and physical findings.

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* Supplied by Geigy Pharmaceuticals, Yonkers, N.Y.

The results of the chronic administration of 200 mg. of the phthalimidine drug to 15 congestive heart failure patients on a Monday, Wednesday, and Friday schedule for 5 weeks is shown in FIGURE 9. There was an average weight loss of 2.8 pounds ($P < 0.01$) at the end of the 5-week period. These patients were on maintenance doses of digitalis; after the first week of administration of the phthalimidine drugs they remained free of edema and symptoms of congestive heart failure with the intermittent dose schedule described. It was not necessary to administer other diuretic agents in addition to this drug in order to maintain the edema-free state. During this study no toxic or side effects were noted in any of the patients. Serum electrolytes including sodium, potassium, chloride, blood urea nitrogen, and CO_2 combining capacity were determined at the beginning and the end of the study, as well as the hemoglobin, hematocrit, and white blood count and differential. There were no significant changes in the electrolytes or the blood counts at the end of the 5-week period.

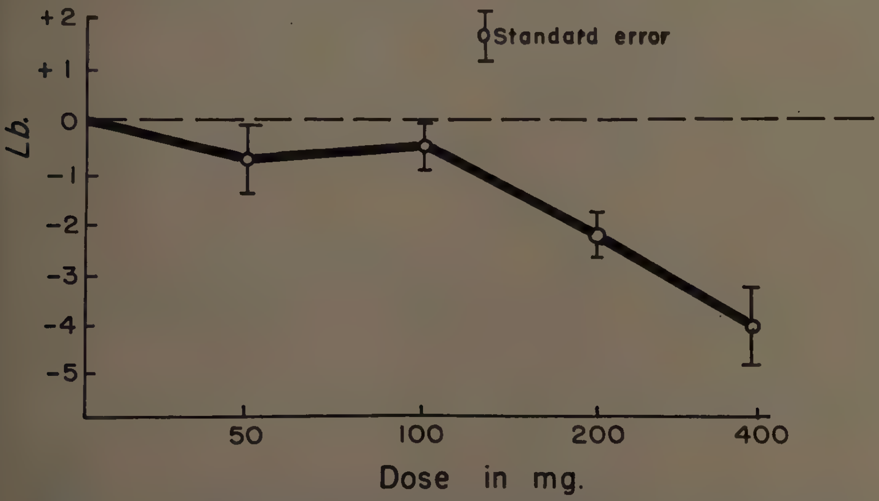

FIGURE 8. Forty-eight-hour weight response to increasing doses of phthalimidine derivative (G 33182) in congestive heart failure patients.

Since these patients maintained good cardiac compensation and remained free of edema on an intermittent dose schedule (Monday, Wednesday, and Friday administration) with the phathalimidine derivative but had required daily administration of other diuretics for similar effects, there appeared to be some basis for considering this drug's activity to be prolonged for periods greater than 24 hours.

In an attempt to provide more definite evidence for this prolonged activity five patients were given a single 200-mg. dose and five patients were given a single 400-mg. dose of the drug. These patients were maintained on a 50 mEq. sodium diet; as a control, 24-hour urinary electrolyte excretion was determined before the single administration of the drug, and daily 24-hour urine electrolytes were determined after the administration of the drug. In FIGURE 10 the 24-hour urinary electrolyte response is shown for the 200-mg. and 400-mg. doses. The sodium excretion with both doses remained above control levels for two 24-hour periods after the single administration of the drug on the first day only. In several patients the sodium excretion remained above control levels during the third 24-hour period. This prolonged response in electrolyte excretion bears out the clinical impression of sustained activity with the phthalimidine diuretic. In the metabolically controlled patient on a 50 mEq. sodium diet, this degree of prolonged activity is not seen with the other major diuretic groups. It is noted in this study that the electrolyte response to the 400-mg. dose is not as great as that with the 200-mg. dose. These findings were also borne out in the dose response curve as determined by electrolyte excretion.

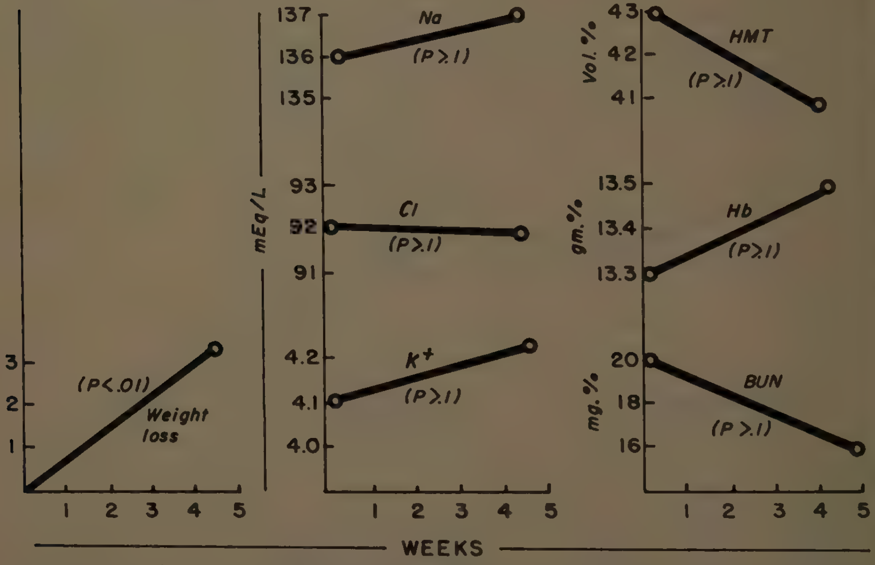

FIGURE 9. The 5-week administration of a phthalimidine derivative (G 33182) in 200-mg doses, given on Mondays, Wednesdays, and Fridays to 15 congestive heart failure patients There is a weight loss of 2.8 lb. at the end of 5 weeks, but no significant change in serum electrolytes and blood count.

A group of patients, free of edema and maintained on a 50 mEq. sodium diet, were given increasing doses of the phthalimidine agent after control 24-hour urine electrolyte excretions were determined. The doses administered were 50 mg., 100 mg., 200 mg., and 400 mg., given as a single morning dose. The 24-hour urine sodium, chloride, and potassium excretions were determined after the administration of the drug and compared with control levels. The results of this study are shown in TABLE 1 and FIGURE 11. A 50-mg. dose in six patients produced a significant sodium and chloride excretion. There is an increasing response in the sodium and chloride excretion up to the maximum effective dose of 200 mg. administered to 11 patients. With the 400-mg. dose the sodium and chloride excretions were not as high as with the 200-mg. dose, but were still of significant levels to produce a good diuretic response. A

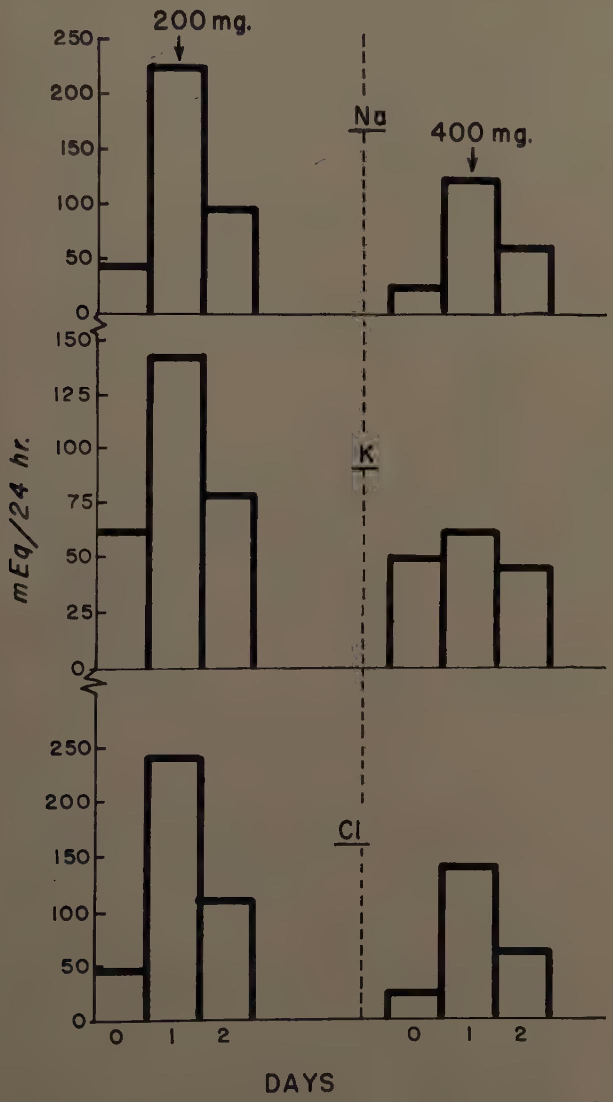

FIGURE 10. Duration of electrolyte excretion after the administration of single 200-mg. and 400-mg. doses of the phthalimidine diuretic, G 33182. The sodium excretion remained above control levels for 48 hours or more. The quantity of sodium excreted with the 400-mg. dose was less than that with the 200-mg. dose.

similar response with very large doses of hydrochlorothiazide had been noted previously.[8] The discrepancies between the sodium response for the 200-mg. and 400-mg. dose, shown in FIGURE 11, and the weight response for these doses, as shown in FIGURE 8, are not incompatible, since in the heart failure patient a 400-mg. dose still produces a significant sodium excretion. In the weight response study it is quite possible that the pathophysiological influence in the patients at the time of administration of the 400-mg. dose were such that a

TABLE 1

Dose in mg.	Sodium			Potassium			Chloride		
	C	D	I	C	D	I	C	D	I
50 mg., 6 patients	42	112	70	65	93	28	46	117	71
St. error			±6.2			±5.0			±10.8
100 mg., 4 patients	52	163	111	83	102	19	47	142	95
St. error			±8.0			±5.8			±18.0
200 mg., 11 patients	46	215	169	53	88	35	47	213	166
St. error			±13.9			±8.1			±14.0
400 mg., 8 patients	43	145	102	42	74	32	52	151	99
St. error			±9.9			±6.0			±12.1

C = control excretion in mEq./24 hours; D = excretion with drug in mEq./24 hours; I = difference of C and D.

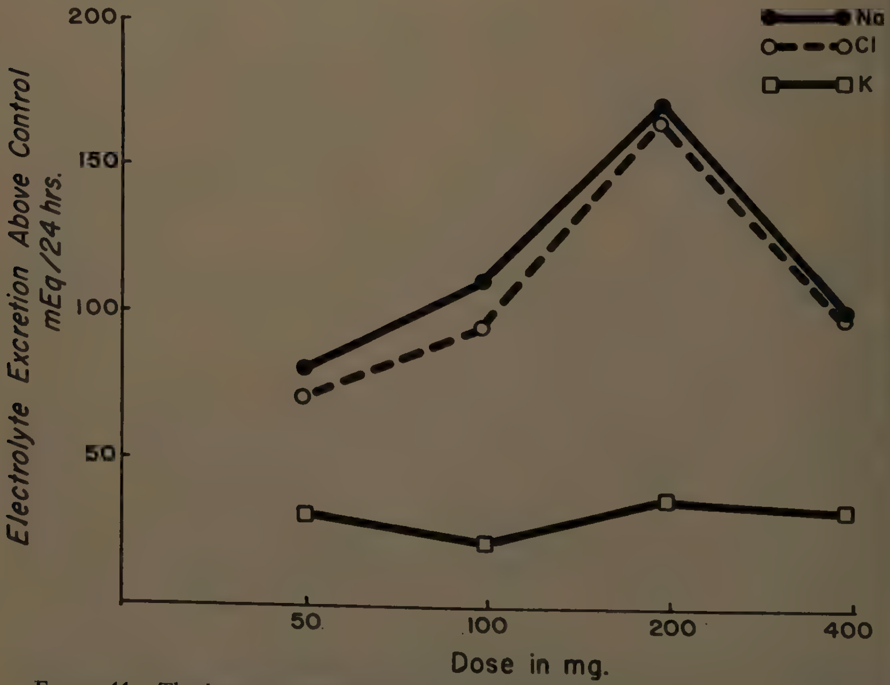

FIGURE 11. The dose response curve of the phthalimidine diuretic, G 33182. The sodium excretion is significant at the 50-mg. dose level, and increases up to the maximum effective dose of 200 mg. The 400-mg. dose produces less sodium excretion than the 200-mg. dose.

significant and greater weight loss was realized than with the 200-mg. dose, since the 400-mg. dose has a significant and potent effect on sodium excretion. However, this discrepancy does point out the difficulty in diuretic evaluation when the pathologic patient is used.

The potassium excretion with increasing doses of this drug is not significantly increased above that with the 50-mg. dose, so that there is a favorable sodium:

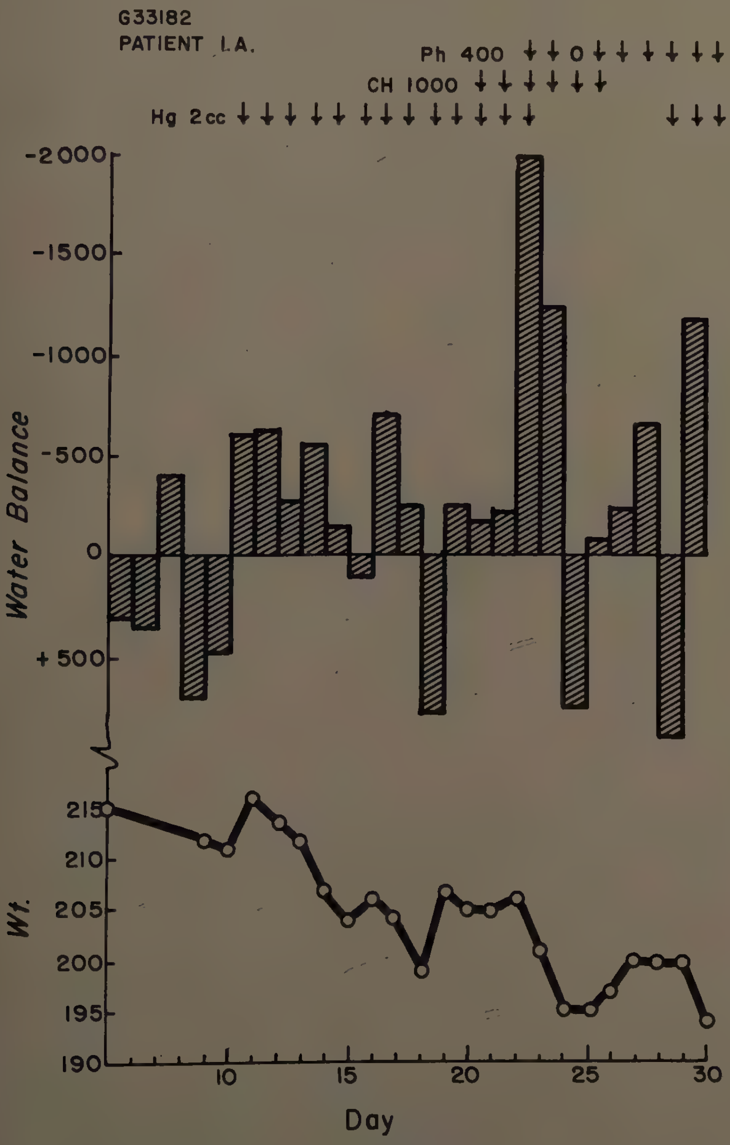

FIGURE 12. Reaction of a patient with idiopathic edema and poor response to chlorothiazide and a mercurial. When 400 mg. of the phthalimidine agent (G 33182) is administered, there is a prompt diuresis, with a negative water balance and a significant loss in weight.

potassium ratio in the urine at the 200-mg. dose level (FIGURE 11). The natriuretic and chloruretic effects of this drug are similar at the dose levels studied.

Apparently, the action of the phthalimidine drug is through its inhibiting effects on enzyme systems at the renal tubular level. Oral administration of the agent produces no significant influence on the renal plasma flow and glomerular filtration rate, but a prompt increase in electrolyte excretion and water diuresis is seen within one hour after administration of the drug.

This drug may be useful in patients whose response to the mercurials and the thiazides is poor. The water balance of a patient with idiopathic edema and a decreasing response to a 1000-mg. dose of chlorothiazide and 2 cc. of mercaptomerin is shown in FIGURE 12. When 400 mg. of the phthalimidine drug is administered there is a prompt increase in urine volume and a negative water balance with a significant weight loss. This may imply a different mechanism of action from the mercurial and the thiazide drugs. This is yet to be substantiated, but the possibility of additive effects through combination of this drug with the other two agents makes one suspect a different mechanism of action. The additive effects of the mercurials and thiazide derivatives have already been cited.

The over-all effects of the phthalimidine diuretic on excretion and clinical response have been quite satisfactory, with no significant side reactions to date. The addition of this agent to the available list of diuretics appears to be a valuable step in the advancement of diuretic pharmacological research.

Summary

A review of the clinical pharmacology of the benzothiadiazines and phthalimidine diuretics is presented. The pharmacological similarities and differences of the various available thiazide drugs are summarized. The pharmacology of the phthalimidine diuretic agent presents the newer aspects of prolonged drug action and the possibility of a different mechanism of action from the thiazides and mercurials.

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COMPARATIVE STUDIES OF THE NEWER DIURETICS

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The large number of currently available diuretics has presented the practicing physician with a bewildering array of claims, facts, figures, and reports. These demand that he either spend much time in comparing individual reports as to potency, side effects, contraindications, and dosages, or that he continue to use the drugs of his past experience and forget the new developments. The problem may be simplified by the availability of comparable quantitative data. The purpose of this report is to quantitatively compare seven diuretics. The seven drugs are: chlorothiazide;[1] hydrochlorothiazide;[2] flumethiazide;[3] hydroflumethiazide;[4] benzydroflumethiazide;[5] trichlormethiazide;[6] and chlorphthalidolone.[7] All drugs were studied using the same facilities and same human bioassay technique, that is, the employment of metabolically controlled conditions for the acute studies.

The methods and materials of this technique have been described fully elsewhere, but briefly include the use of at least 10 subjects with hypertensive cardiovascular disease who had previously been in congestive heart failure, but at the time of study are not in failure and have no detectable edema. These patients continue to receive all previous medication for control of their congestive heart failure (except diuretics) and are maintained under metabolically controlled conditions, receiving 3.0 l. distilled water and 50 mEq. sodium diet per day. They are given incremental doses of the drug, with adequate time for equilibration between each dose, until a dose response curve has been obtained. Following the determination of the dose response curve they each receive both the minimum and maximum effective dose; by use of an analysis of variance and comparing the observed response to the known response to intramuscular meralluride (Mercuhydrin), a determination of (relative) potency is obtained.

Fractional urines are obtained after single minimum and maximum effective doses to determine the electrolyte excretion pattern. The drug is then administered continuously and observations made as to daily body weight, urinary sodium excretion, and serum biochemical architecture. Next, the efficacy of the drug in various edematous states is observed, as is its efficacy as an antihypertensive agent and/or as an adjunct to antihypertensive therapy. An additional observation includes the 24-hour excretion of sodium and potassium in a group of patients receiving chlorothiazide, trichlormethiazide, and chlorphthalidolone at the end of six months of therapy.

This method of bioassay has been questioned. However, adequate metabolic control, even with such a small number of subjects, can provide statistically valid results and this provides a great degree of reproducibility, consistent experimental design, and an adequate basis for quantitative evaluation of the drug responses. Small discrepancies may arise when these results are transferred to a large outpatient clinic with the inevitable loss of precise control, variable diet, drug absorption, degree of completeness in following therapeutic instructions, and clinical status of the patients.

Figure 1 presents the various dose response curves of the diuretics, and not only demonstrates the wide range of potency per milligram but also the increased natriuretic potency per maximum effective dose. The great similarity in the shape of the curves is a reflection of their probable common site of action and biochemical effect. The comparative electrolyte excretion patterns after a single maximum effective dose of the drugs is presented in figure 2. Again, note that as refinements have occurred there is, concomitant with the increased natriuretic potency, a decreased tendency toward potassium wastage. This factor cannot be entirely disregarded with any of these agents. In general, the drugs reach a maximum peak of action within 12 hours and show no significant effect on urinary electrolyte excretion at the end of 24 hours. However, it has been noted that chlorphthalidolone has a duration of action of at least 48 hours and trichlormethiazide of approximately 36 hours. The urinary sodium excretion in relation to potassium, noted after administration of these agents, is important, particularly in light of case reports of clinically significant hypokalemia secondary to administration of these drugs. Figure 3 presents

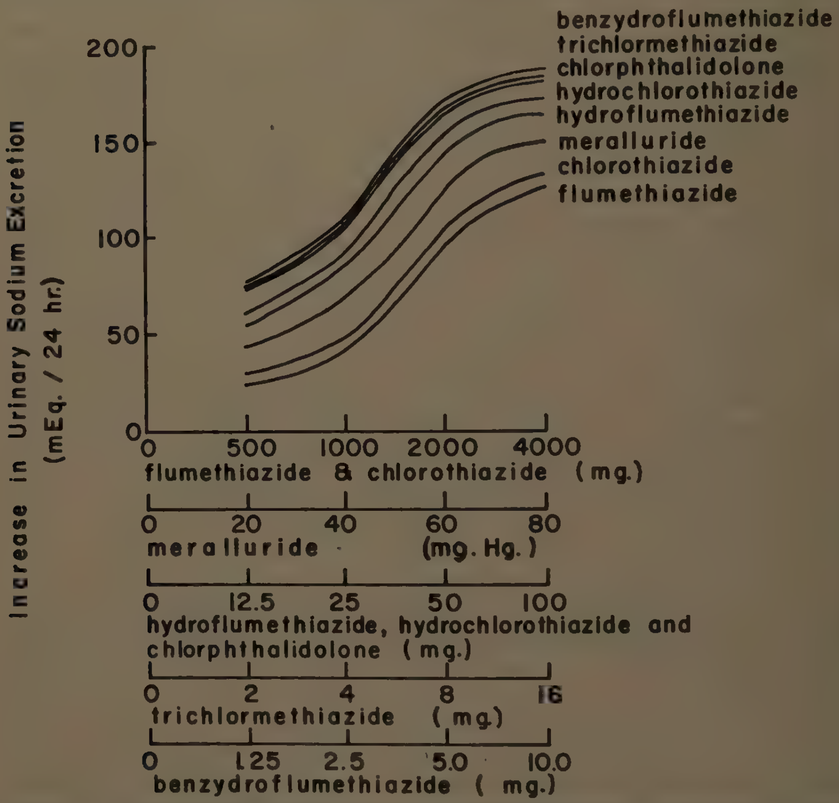

Figure 1. Comparative dose response curves of various diuretics, demonstrating the wide range of potency per milligram and the increased natriuretic potency per maximal effective dose.

the initial and long term urinary relationship of sodium to potassium noted with three of these agents using one-half maximum clinical dosages. Acutely, the sodium:potassium ratio tends to be proportional to the natriuretic potency of the drug. Chronically, however, with chlorothiazide the urinary sodium:potassium ratio approaches one after the nonfixed sodium stores of the body are depleted. The ratio of sodium:potassium in the urine following six months therapy with trichlormethiazide was two, and following chlorphthalidolone was three. It is of further interest that prior to any diuretic therapy, random cardiac patients demonstrated a urinary sodium:potassium ratio of less than one (0.7, the average for 100 patients).

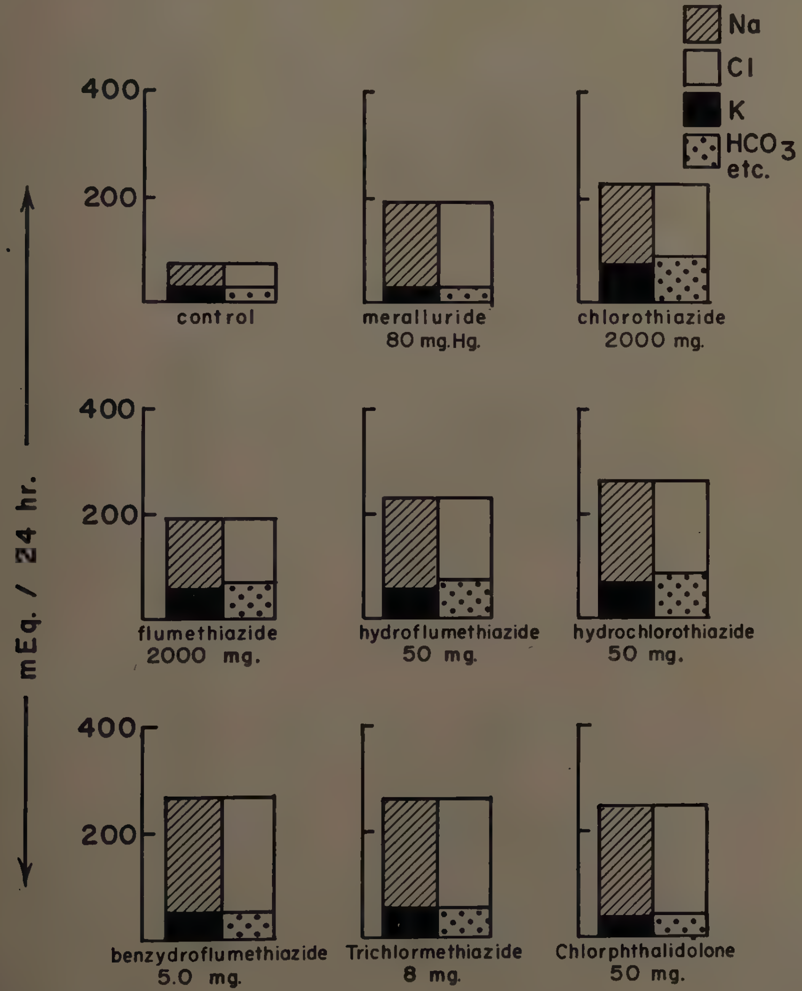

FIGURE 2. Urinary electrolyte excretion patterns following single doses of various diuretics demonstrating that as refinements have occurred there is a decreased tendency toward potassium wastage.

Further studies indicate that this drug-induced potassium loss is not affected by dietary sodium or potassium but is a reflection of the drug dosage. Such factors as over-dosage can thus lead to clinical hypokalemia, the acute manifestations of which may be cardiac arrhythmias. A chronic, low grade, potassium wastage leads to development of general malaise, leg cramps, weakness, nausea, and vomiting, and these may have superimposed acute hypokalemic manifestations. We have found that supplementary potassium is rarely required if the drugs are properly used and a diet adequate in meat and fruit is consumed.

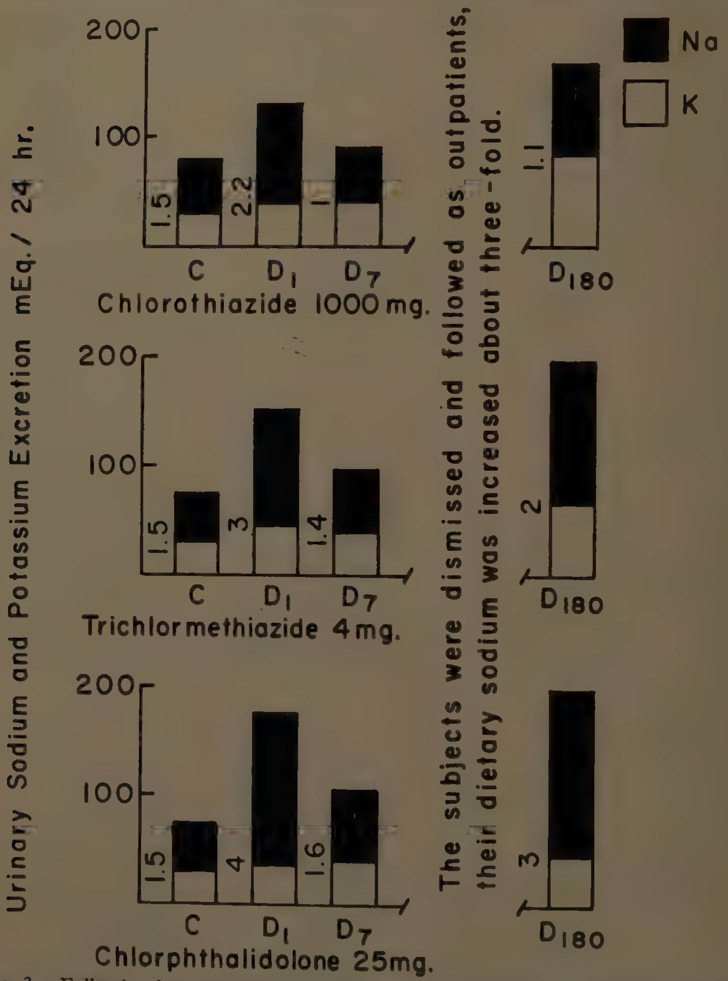

FIGURE 3. Following long-term therapy the excretion of sodium in relation to potassium tends to follow, but not parallel, the natriuretic potency of the drug. The effects of acute and chronic therapy with three diuretics on the urinary excretion of sodium and potassium.

Other electrolyte excretion effects are generally those of increased *p*H and bicarbonate excretion (especially with the earlier-developed drugs). Increased chloride excretion generally parallels the sodium excretion. The later-developed derivatives (hydroflumethiazide, trichlormethiazide, chlorphthalidolone, and benzydroflumethiazide) have a more singularly saluretic effect with small changes in urinary *p*H or in bicarbonate excretion. With daily administration, all of these drugs are continually effective, producing a progressive loss of body weight without significant alteration in serum electrolytes, blood urea nitrogen or hematocrit (FIGURE 4).

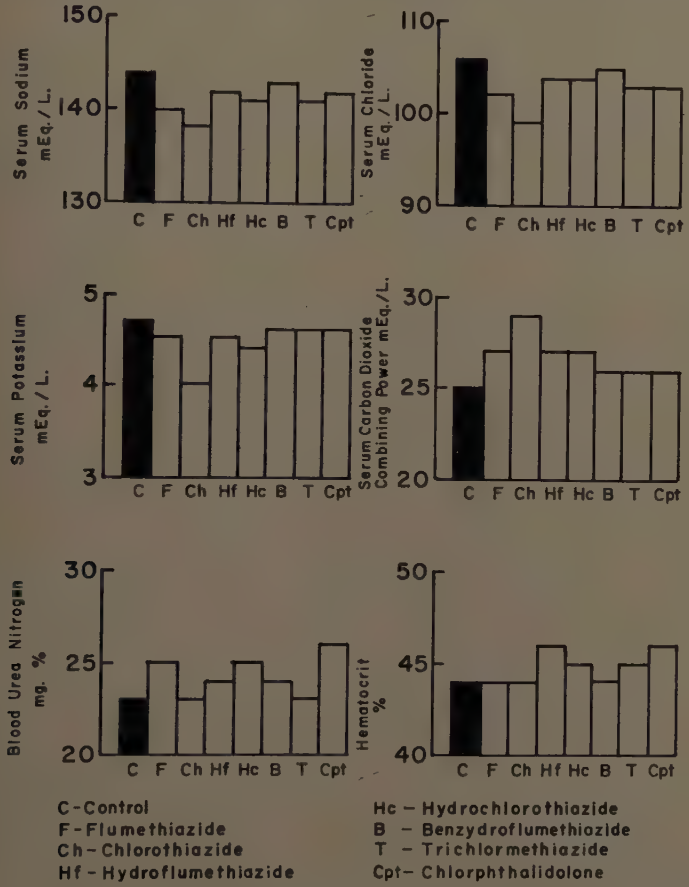

FIGURE 4. With daily administration the diuretics under consideration are continually effective without producing significant alteration in serum electrolytes, blood urea nitrogen, or hematocrit. Composite figure demonstrating the effect of serum electrolytes, blood urea nitrogen, and hematocrit following seven days of continuous therapy with various diuretics using maximal effective doses.

The value of these compounds in antihypertensive therapy indicates some correlation with natriuretic activity, but there appears to be a limit of a decrease 20 to 23 mm. Hg in the hypotensive effect except, perhaps, in the case of chlorphthalidolone. The hypotensive effect is not necessarily associated with a decrease in body weight.[8]

Although parenterally administered mercurials are often still the therapy of choice in acute edematous-hypertensive states, the ease of administration and diuretic potency of these diuretics makes them a valuable therapeutic tool, particularly in long-term therapy.

Summary

The dose response curves, relative potency, electrolyte excretion patterns, effect of continuous administration on body weight and serum biochemical architecture, and efficacy in various edematous states and as an adjunct and agent in antihypertensive therapy of seven diuretics have been compared.

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MODE OF ACTION AND CLINICAL USEFULNESS OF ALDOSTERONE ANTAGONISTS*

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With few exceptions the development of clinically significant edema depends upon the coexistence of two factors: (1) sodium-retaining corticosteroids such as aldosterone, and (2) a circulatory disorder characterized by abnormal pressure relationships between the extravascular fluid compartment and the venous circulation. Thus in congestive heart failure edema forms, in part, because of an increase in venous pressure. In hepatic cirrhosis ascites develops, in part, because of an increase in portal venous pressure. In hypoalbuminemic disorders such as nephrosis edema forms, in part, because of diminished oncotic pressure within the intravascular compartment.

Even in the presence of such circulatory disorders, however, edema would not be a problem were it not for the sodium-conserving action of corticosteroids. Aldosterone secretion is frequently elevated in patients with edema, but even "normal" levels of aldosterone are sufficient to permit edema formation if circulatory factors are conducive. On the other hand, in the total absence of aldosterone (as in adrenalectomized patients maintained on cortisol alone) it is easy to induce a negative sodium balance even in patients with cirrhosis, hypoalbuminemia, or congestive heart failure. That an excess of aldosterone is not sufficient to cause edema in the absence of a circulatory disorder is evidenced by the fact that patients with primary hyperaldosteronism rarely have significant edema unless cardiac or renal failure supervenes.[1]

In view of the essential role of aldosterone in the pathogenesis of edema, it seemed reasonable to attempt to treat edematous patients with an aldosterone antagonist. This approach had its beginning in the work of Landau *et al.*, who observed that progesterone antagonized the sodium-retaining action of desoxycorticosterone.[2] The carefully designed studies of Kagawa *et al.*[3] then established the fact that certain steroidal lactones were capable of antagonizing the sodium-retaining and potassium-wasting actions of desoxycorticosterone and aldosterone. The unique function of the steroidal lactones could not have been discovered in the routine screening of steroids. Inasmuch as the steroidal lactones have little or no effect on electrolyte excretion in the adrenalectomized animal, it was necessary to pretreat the test animals with a mineralocorticoid before the characteristic properties of the steroidal lactones could be observed.

It was subsequently demonstrated that steroidal lactones were effective in antagonizing the sodium-retaining action of desoxycorticosterone and aldosterone in human subjects.[4,5] The original compound in this series, SC 5233 (FIGURE 1), was effective only when administered intramuscularly in dosage of at least 600 mg., or orally in dosage of several grams daily. Since synthesis of SC 5233 was expensive, this particular compound did not appear to be prom-

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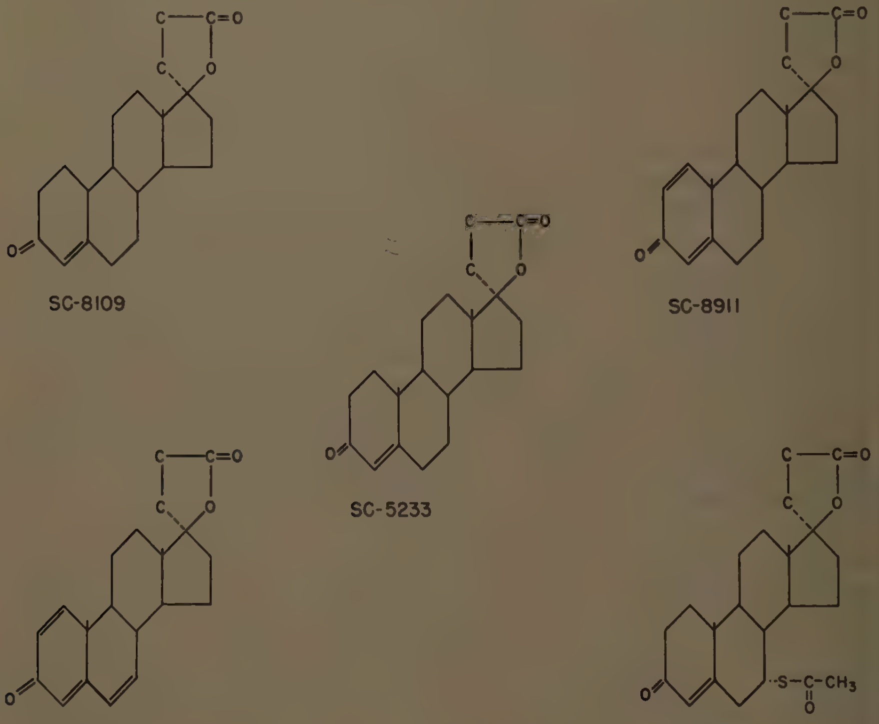
ising as a practical therapeutic agent. Kagawa *et al.* and their associates then directed their attention to the search for compounds that would be orally effective and of greater potency than was SC 5233. Thus far four derivatives of SC 5233 have become available for clinical evaluation. Their chemical structures are depicted in FIGURE 1. The distinctive structural feature common to all of these compounds is the "spirolactone" configuration at position 17 of the steroid molecule. The generic term spirolactone is often applied to this entire group of compounds.



SC-8109

SC-8911

SC-5233

SC-9456

SC-9420
SPIRONOLACTONE

FIGURE 1. Chemical structures of the spirolactone compounds.

SC 8109, the 19-nor derivative of SC 5233, proved to be many times more potent than SC 5233 itself, and was found to be effective in dosage as low as 400 mg./day orally or 100 mg./day intramuscularly.

SC 9420, the 7-acetylthio derivative of SC 5233, was found to be effective in dosage as low as 100 mg./day orally. This compound has been widely used under the official name of spironolactone and the proprietary name Aldactone.

SC 8911, the 1-2-dehydro derivative of SC 5233, was found to be much more potent than SC 5233 itself; it is effective in dosage as low as 100 mg./day orally.

SC 9456, the 6-7-dehydro derivative of SC 8911, was found to be less potent than SC 8911 itself, but more effective than SC 5233.

All of the spirolactones studied are qualitatively similar in their effects on electrolyte excretion. The precise explanation of their quantitative (potency) differences is as yet unknown.

Mechanism of Action

The concept that the spirolactones act by antagonizing the renal tubular action of aldosterone or similar mineralocorticoids is based on the following observations:

(1) The spirolactones have little or no effect on urinary electrolytes in the absence of aldosterone or similar mineralocorticoids. This was clearly shown by Kagawa *et al.* in their original studies of rats[3] and has been confirmed by studies of adrenalectomized dogs and patients with Addison's disease in this laboratory.[4,5] When, however, spirolactones are given to subjects with intact adrenal function or to patients with Addison's disease, who are maintained on exogenous mineralocorticoid, a pronounced change in urinary electrolytes is produced.

(2) The electrolyte excretion pattern produced by spirolactones is similar to that resulting from the abrupt withdrawal of aldosterone[5] or that produced by the administration of compounds (such as amphenone B and SU 4885) that interfere with adrenocortical biosynthesis of aldosterone.[6] Thus aldosterone administration results in *decreased* urinary excretion of sodium and chloride and *increased* excretion of potassium, titratable acid, and ammonium. Aldosterone withdrawal, inhibition of aldosterone synthesis, and spirolactone administration all result in *increased* sodium and chloride excretion and *decreased* potassium, titratable acid, and ammonium excretion. Spirolactones are unique among diuretic agents in antagonizing *all* of the effects of aldosterone.

(3) The spirolactones do not decrease the adrenocortical secretion of aldosterone or other steroids, judging from studies of aldosterone secretion rate, urinary levels of aldosterone, urinary levels of the tetrahydro metabolite of aldosterone, urinary 17-ketosteroid levels, or urinary 17-hydroxycorticoid levels. These studies are described in detail elsewhere.[7,8] The effect of spirolactones on electrolyte excretion therefore cannot be explained on the basis of possible interference with adrenal steroid production.

(4) As demonstrated by Wiggins *et. al.*,[9] the spirolactones do not exert a significant effect on glomerular filtration rate.

Clinical Usefulness of Spirolactone

A natriuretic response to spirolactone (FIGURE 2) is observed in all forms of edema as long as severe renal insufficiency is not present. In general, however, a spirolactone is only moderately effective when used as the sole diuretic agent, and at times a greater and more rapid diuresis can be accomplished by conventional agents. The practical therapeutic merits of the spirolactones derive from two facts:

First, the fact that the mechanism of action of spirolactone differs from that of any type of diuretic makes it possible that the spirolactones act synergistically with other diuretics, particularly in patients who have developed refractoriness to conventional diuretics.

Second, the fact that the spirolactones oppose the potassium-wasting influence of aldosterone makes them of unique value in the treatment of patients with secondary hyperaldosteronism, who frequently respond to conventional diuretics by excreting undesirably large quantities of potassium.

In the initial phase of treatment of an edematous patient with conventional diuretics, sodium is usually the major cation to be lost. As sodium is lost from the body, aldosterone secretion rises to progressively higher levels even before the edema has been completely corrected.[10] In the presence of high aldosterone levels, conventional diuretics induce relatively more potassium loss and relatively less sodium loss than when aldosterone levels are low. Administration of spirolactone tends to oppose the action of aldosterone, so that conventional diuretics continue to promote sodium excretion with relatively little potassium wasting. Unfortunately, however, the spirolactones usually do not *completely* abolish the kaliuretic response to conventional diuretics.

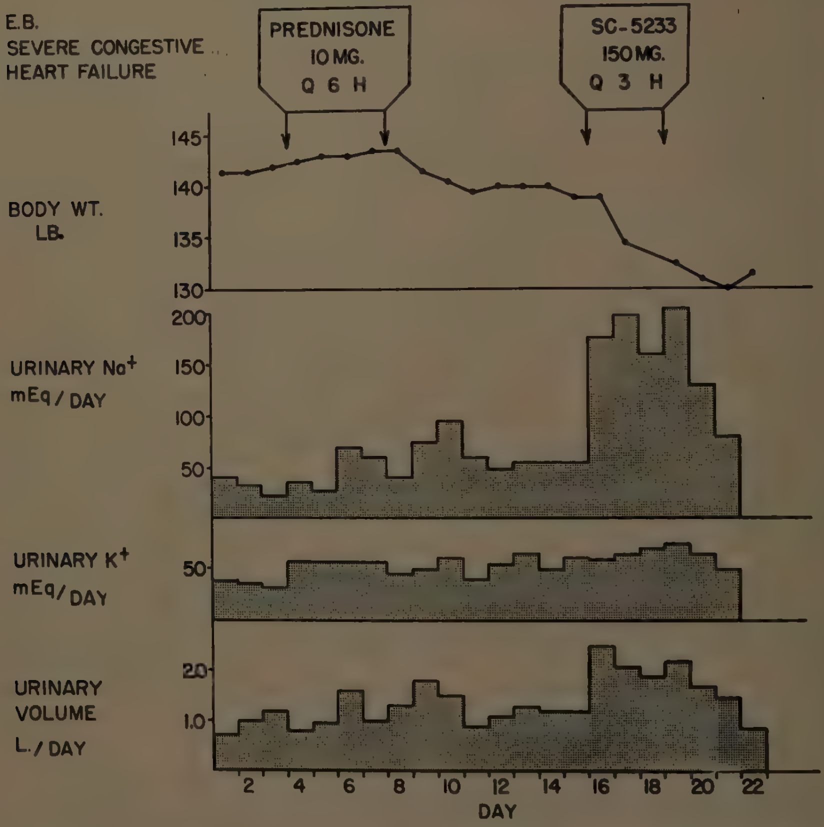


FIGURE 2. Responses to prednisone and to spirolactone in a patient with congestive heart failure. Prednisone produced little increase in urinary volume and sodium, while spirolactone induced a brisk diuresis and a 10-pound weight loss.

Some of these points are illustrated in FIGURE 3. The patient was a young woman with postnecrotic cirrhosis. Ascites had not been controlled by mercurials or chlorothiazide and had required multiple paracenteses. A portocaval shunt previously had been performed for bleeding esophageal varices. Urinary aldosterone excretion was markedly elevated. Urinary sodium excretion was less than 1 mEq./day regardless of sodium intake. When spirolactone alone was administered there was a manyfold increase in urinary sodium, although the absolute increase in sodium excretion was modest. There was no change in urinary potassium. When a benzothiadiazine derivative (P-1393, 3-benzylthiomethyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide) was administered alone, the most striking change was a marked increase in urinary potassium excretion, while urinary sodium was barely altered. When, however, spirolactone was given in the presence of P-1393, there resulted a prompt and impressive sodium diuresis, while urinary potassium excretion fell to approximately one half of the base line level (that is, the patient actually *retained* potassium). During the period of combined drug therapy the patient lost 10 pounds in weight.

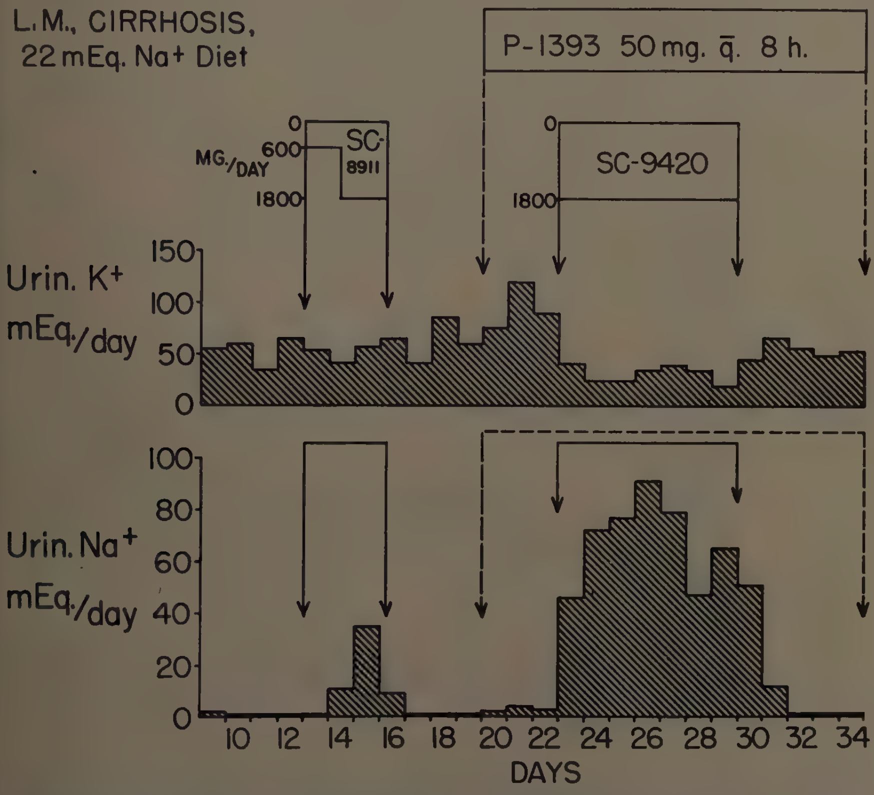


FIGURE 3. Responses to spirolactone and a benzothiadiazine derivative, alone and in combination, in a patient with cirrhosis and ascites; note the considerable natriuretic response to combination therapy while potassium loss actually decreased.

The advantages and effectiveness of the long-term use of spirolactones in combination with other diuretics are illustrated in FIGURE 4. Following paracentesis the same patient described above was discharged from the hospital on low-salt diet and a combination of spirolactone and P-1393 for three days of each week. For three months she maintained her "dry" weight on this program. At the end of three months spirolactone was withdrawn, while P-1393 was continued. Almost immediately the patient began to gain weight. Resumption of spirolactone in the previous maintenance dosage slowed but did not completely halt the weight gain. Increase in dosage, however, resulted in diuresis with loss of 14 pounds of fluid. During the year prior to spirolactone and P-1393 therapy, paracentesis had been necessary every four to eight weeks. This patient has now been followed for more than one year on spirolactone and P-1393 therapy three days weekly. She is active, employed in a factory 40 hours weekly, and has required no further paracenteses. Her serum electrolytes are normal. The basic disease process, however, has not improved, judging from persistent abnormalities of hepatic function.

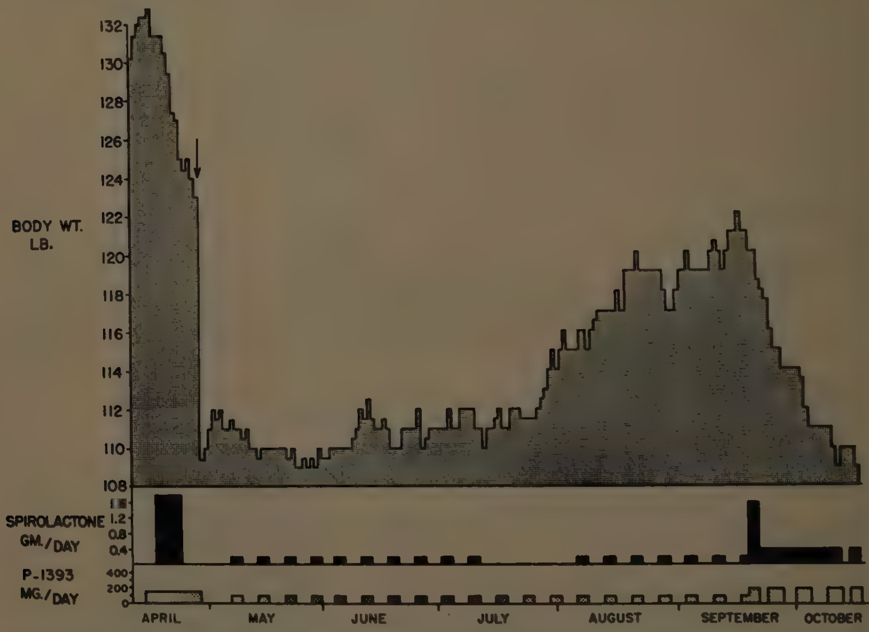


FIGURE 4. Results of long-term treatment of the same patient as shown in FIGURE 3. The arrow indicates the point at which paracentesis was performed.

Summary

A number of steroid 17-spirolactones have proved to be effective diuretic agents in man and have been demonstrated to exert their effects by antagonizing the renal tubular action of aldosterone. The following evidence supports the view that the spirolactones act as aldosterone antagonists.

(1) The spirolactones are effective only in the presence of aldosterone or aldosteronelike steroids, whether endogenous or exogenous.

(2) The effects of the spirolactones are similar to those observed with the acute withdrawal of exogenous aldosterone or acute suppression of endogenous aldosterone, that is, increased excretion of sodium, chloride, and water, and decreased excretion of potassium, titratable acid, and ammonium.

(3) The spirolactones do not block the secretion of aldosterone or other corticosteroids.

(4) The spirolactones do not appreciably modify glomerular filtration rate.

When administered to patients with edema, the spirolactones may induce satisfactory diuresis if employed alone, but they are of greatest therapeutic value when used in combination with other diuretic agents. Conventional diuretics cause potassium loss in addition to sodium loss. The addition of a spirolactone tends to augment the natriuretic while diminishing the kaliuretic effects of conventional diuretics. Patients have been maintained on combined therapy with spirolactone and chlorothiazide derivatives for as long as one year without developing refractoriness to the regimen or significant electrolyte imbalance.

Acknowledgments

Grateful acknowledgment is extended to Clarence Gantt of G. D. Searle & Co., Skokie, Ill., for generously providing the spirolactones employed in this study. P-1393 was made available through the kindness of Domenic Iezzoni of Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

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EFFECTS OF BENZOTHIADIAZINES ON SERUM AND TOTAL BODY ELECTROLYTES*

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The management of hypertensive disease and of various edematous states has witnessed an important advance with the introduction of the benzothiadiazines.[1] The effects of these agents on serum potassium concentration and on other aspects of electrolyte metabolism have been well documented.[2-6] These include hypochloremic alkalosis, hypokalemia, azotemia, and hyperuricemia.

Studies performed in this laboratory have demonstrated that a decrease in serum potassium concentration occurs in approximately 85 per cent of patients receiving any of the benzothiadiazines. Simultaneous determinations of total body potassium utilizing the isotope dilution technique, however, have revealed no significant changes in this parameter.[7] This suggested that the hypokalemia associated with benzothiadiazine administration reflects a redistribution of potassium rather than a frank depletion of this cation. An inverse relationship between extracellular potassium concentration and *p*H has been demonstrated by numerous investigators.[8-13] Consequently, the current study was undertaken in order further to evaluate these changes in potassium metabolism and to elucidate the mechanisms producing hypokalemia during benzothiadiazine therapy.

Methods

Patients for these studies were selected at random from the Hypertensive Clinic of the Loyola University–Mercy Hospital Clinics. All patients utilized for these studies had hypertensive disease of moderate severity, as judged from the level of the mean blood pressure, the degree of renal functional impairment, the heart size (determined by X ray), the electrocardiogram, and the appearance of the optic fundi. None of these patients was in the malignant or accelerated phase of hypertensive disease at the time of these studies, and none had overt evidences of congestive heart failure such as orthopnea or peripheral edema. All electrolyte studies were performed when the patients were in the postabsorptive state.

At the initiation of studies of each patient, the height, basal weight, and resting blood pressure were determined. Following this, a sample of arterialized venous blood was drawn under oil with minimal stasis, and the exchangeable potassium was then determined by methods previously described.[14]

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The investigation was conducted during the tenure of A. J. Carballo's postdoctoral research fellowship from the National Heart Institute, Public Health Service, Bethesda, Md., under Research Grant HF-9345.

The patients were studied before and immediately after each of the programs of therapy listed in TABLE 1.* In the group of 20 patients that received hydrochlorothiazide alone, 100 mg. daily, standard 12-lead electrocardiograms were taken before and after the period of therapy. An additional group of nine patients was studied to evaluate the effects of supplementary sodium chloride intake. In this group of patients, base line studies of weight, blood pressure, serum electrolytes, and total body potassium were done initially. Following this, hydrochlorothiazide in doses of 100 mg. was administered daily for two weeks, when the weight, resting blood pressure, and serum electrolyte concentrations were determined. Following this, supplementary sodium chloride was administered in the form of Thermotabs† in doses of 2.7 gm. daily for 14 days, and the electrolyte determinations were again performed. Finally, the patients were given 4.5 gm. of supplementary sodium chloride for 14 days, and the studies were repeated.

Serum *p*H was determined with a Coleman Model 18 *p*H meter, serum bicarbonate by the manometric method of Peters and Van Slyke,[15] serum chloride by the Wilson and Ball modification[16] of the Van Slyke method,[17] sodium and potassium were determined with an internal standard flame photometer,‡ and the blood urea nitrogen was determined by the method of Barker.[18] Assays for radioactivity were performed with a well-type scintillation counter utilizing a Lucite crystal. Exchangeable potassium was calculated by methods previously described.[14]

TABLE 1
PROGRAMS OF THERAPY

No. patients	Medication	Dose (mg./day)	Added salts	Dose (gm.)	Duration of therapy (days)
20	Hydrochlorothiazide	100	None	—	28
17	Benzydroflumethiazide	10	None	—	28
10	Hydrochlorothiazide	100	KCl	0.6	28
10	Hydrochlorothiazide	50	KCl	0.6	28
14	Hydrochlorothiazide	100	NH_4Cl	1.0	28

Results

The results obtained in these studies are listed in TABLES 2 through 9 and in FIGURES 1 through 7.

Weight. None of the 80 patients utilized in this study was clinically edematous at the time the initial determinations were made. As a result, although

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* The hydrochlorothiazide and the hydrochlorothiazide combined with potassium chloride were supplied by Edmund de Maar, of Merck Sharp & Dohme Research Laboratories, West Point, Pa. The benzydroflumethiazide was supplied by R. C. Merrill, of the Squibb Institute for Medical Research, New Brunswick, N. J.

† Thermotabs were supplied, through the courtesy of Richard Smith, by Merck Sharp & Dohme Research Laboratories, West Point, Pa. Each tablet contained 0.45 gm. sodium chloride, 30 mg. potassium chloride, 18 mg. calcium carbonate, and 0.2 gm. dextrose.

‡ Advanced Instruments, Inc., Newton Highlands, Mass.

TABLE 2

OBSERVATIONS ON 20 PATIENTS WITH HYPERTENSIVE HEART DISEASE AND NO EDEMA, FOLLOWING ADMINISTRATION OF HYDROCHLOROTHIAZIDE FOR 28 DAYS*

Pat't	Age (yr.)	Sex	Ht. (cm.)	Weight (kg.)		Serum *p*H (mEq./l.)		Serum HCO_3^- (mEq./l.)		Serum Cl^- (mEq./l.)		Serum Na^+ (mEq./l.)		Serum K^+ (mEq./l.)		BUN (mg./100 ml.)		K^E (mEq.)		B.P. (mm. Hg) Bef.	Mean B.P. (mm. Hg) Bef.	B.P. (mm. Hg) Aft.	Mean B.P. (mm. Hg) Aft.
				Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.				
L.R.	58	M	168	70.7	69.5	7.34	7.37	28.6	32.6	100	95	143	135	4.50	3.66	18	19	2942	2757	170/100	123	180/100	127
F.C.	59	F	135	66.0	63.3	7.24	7.31	25.0	27.2	106	103	137	147	4.45	3.57	25	29	2421	2144	240/120	160	145/110	135
E.K.	36	M	169	61.4	56.4	7.34	7.44	28.6	33.5	104	96	137	146	4.00	2.75	14	21	2993	2694	180/135	150	145/110	122
A.L.	40	F	135	59.3	56.4	7.39	7.43	29.0	33.5	101	96	145	146	3.00	2.75	22	21	1964	1708	260/150	187	195/110	138
O.W.	64	F	144	60.9	58.2	7.35	7.37	29.0	29.5	107	95	139	137	5.02	3.47	13	22	2393	2091	220/150	143	165/110	122
L.B.	58	F	150	61.5	60.3	7.30	7.35	29.9	29.9	102	96	148	143	4.73	4.35	14	25	2036	2008	190/110	137	180/95	123
S.D.	50	M	176	82.0	81.0	7.27	7.33	21.7	32.1	103	92	144	138	4.75	4.34	14	25	3385	3790	230/150	177	210/120	150
E.G.	36	M	174	75.6	73.4	7.35	7.45	31.3	35.3	103	92	138	135	4.93	3.04	9	16	3505	3403	170/130	143	160/120	133
A.D.	45	M	170	75.7	75.0	7.31	7.43	29.0	33.0	104	96	141	144	4.65	4.03	12	15	3605	3546	205/115	145	180/105	130
G.W.	58	M	182	63.2	63.4	7.37	7.35	29.5	28.1	100	99	140	145	3.53	4.26	14	10	2609	3169	260/140	180	210/120	150
J.S.	52	M	178	93.2	91.1	7.31	7.38	27.2	29.1	96	93	147	145	4.45	4.04	22	23	3650	4175	210/114	146	210/115	147
E.G.	45	F	163	66.5	66.7	7.35	7.45	25.4	26.8	101	101	142	148	4.50	4.02	14	14	2143	2622	240/140	173	210/120	150
A.H.	59	F	164	71.1	71.3	7.37	7.38	26.3	27.3	100	102	148	147	4.40	4.58	10	9	1980	2107	180/115	137	175/110	132
L.A.	49	F	163	82.3	83.4	7.39	7.43	22.8	30.0	97	103	147	147	4.04	4.60	26	26	2169	2626	210/130	157	150/90	110
M.M.	39	F	163	93.3	94.2	7.37	7.46	24.6	35.9	102	89	143	145	4.18	3.18	20	15	2791	2667	160/130	140	145/110	122
R.P.	56	M	179	83.1	86.3	7.33	7.36	31.3	27.7	101	99	140	142	4.52	4.40	16	17	2849	3090	235/130	165	220/115	150
J.R.	60	F	158	60.0	56.7	7.39	7.44	24.6	31.7	105	94	145	142	5.02	4.18	11	17	1854	1804	170/96	121	140/95	110
I.M.	64	F	168	115.2	115.3	7.25	7.32	27.2	28.6	101	96	138	145	4.60	4.13	16	22	3521	3606	265/110	162	200/100	133
E.H.	34	F	156	67.7	65.9	7.27	7.35	22.3	29.0	107	95	134	140	4.47	3.72	13	19	2764	2579	180/125	143	180/120	140
D.D.	43	F	170	60.9	60.1	7.31	7.50	22.3	27.2	104	96	133	140	4.64	3.40	15	18	2319	2280	160/110	127	130/105	113
Mean				73.5	72.4	7.33	7.40	27.1	30.4	102	96	141	143	4.42	3.82	16	19	2695	2743		151		132
S.D.				14.6	15.5	0.05	0.05	2.8	2.8	3	4	5	4	0.49	0.58	5	5	599	697		19		13

* Daily dose 100 mg.; Bef., before treatment; Aft., after treatment.

TABLE 3

OBSERVATIONS ON 17 PATIENTS WITH HYPERTENSIVE HEART DISEASE AND NO EDEMA, FOLLOWING ADMINISTRATION OF BENZYDROFLUMETHIAZIDE FOR 28 DAYS*

Pat't	Age (yr.)	Sex	Ht. (cm.)	Weight (kg.)		Serum *p*H (mEq./l.)		Serum HCO_3^- (mEq./l.)		Serum Cl^- (mEq./l.)		Serum Na^+ (mEq./l.)		Serum K^+ (mEq./l.)		BUN (mg./100 ml.)		K^E (mEq.)		Mean B.P. (mm. Hg)	
				Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.
B.N.	56	F	155	81.0	77.6	7.36	7.39	28.1	28.9	107	100	131	137	3.36	3.62	13	21	2005	2333	123	127
J.H.	60	F	158	54.1	54.4	7.45	7.48	25.1	23.9	104	106	127	138	4.17	4.10	20	26	1723	2093	127	102
W.H.	37	M	175	90.7	80.6	7.35	7.40	28.0	26.8	105	99	135	135	4.60	4.00	10	15	3581	3613	130	120
E.B.	58	F	158	55.9	53.8	7.35	7.39	27.8	25.3	103	101	137	137	4.68	4.02	17	15	2046	2206	152	153
K.D.	62	F	150	66.6	65.7	7.36	7.35	27.3	28.2	103	98	136	134	4.36	4.08	4	10	1941	2015	135	143
W.A.	40	M	165	110.0	114.1	7.30	7.38	24.8	27.7	109	101	144	137	4.76	4.37	12	15	3669	3661	119	127
I.F.	57	F	165	70.1	67.3	7.37	7.39	25.9	29.9	105	101	131	136	4.85	4.38	14	21	2239	2165	110	130
I.M.	37	F	153	57.3	56.5	7.46	7.48	23.7	27.9	105	102	137	135	3.90	3.54	3	9	2005	1977	138	123
C.S.	46	F	153	82.6	83.6	7.32	7.38	31.2	29.9	104	102	137	137	4.62	3.14	24	18	2584	2528	145	163
O.H.	54	F	153	74.8	74.9	7.49	7.50	22.0	27.7	101	105	131	136	5.00	3.36	18	16	2212	1968	147	153
A.W.	59	F	163	73.4	75.0	7.35	7.46	28.1	30.1	103	104	137	135	3.50	3.84	15	11	3612	3599	166	143
C.R.	59	F	166	63.5	62.8	7.29	7.37	23.9	31.1	103	99	139	134	4.83	4.13	16	22	1965	1959	135	112
J.S.	65	M	163	85.0	82.7	7.37	7.39	26.6	24.8	102	101	135	133	4.00	3.85	27	21	3126	3001	110	116
I.L.	52	F	155	101.5	105.2	7.41	7.44	27.6	29.8	105	103	145	144	4.80	3.92	20	9	2866	2794	137	133
E.G.	45	F	161	70.9	70.7	7.37	7.45	26.1	28.8	106	103	142	142	4.80	3.48	13	14	2575	2549	160	156
A.Mc.	47	F	151	100.0	98.4	7.31	7.40	24.8	29.8	106	98	145	137	5.00	4.31	21	15	2559	2488	133	143
J.Mc.	58	M	165	60.1	59.4	7.33	7.42	27.9	31.1	106	101	147	140	4.55	3.62	12	9	2637	2477	120	130
Mean				76.3	75.5	7.37	7.42	26.4	28.3	105	101	137	137	4.46	3.87	15	16	2550	2554	135	134
S.D.				16.9	17.6	.06	.04	2.2	2.1	2	2	6	3	.50	.36	6	5	620	590	16	17

* Daily dose 10 mg.; Bef., before treatment; Aft., after treatment.

Table 4

Observations on 10 Patients with Hypertensive Heart Disease and No Edema, Following Administration of Hydrochlorothiazide together with Potassium Chloride for 28 Days*

Pat't	Age (yr.)	Sex	Ht. (cm.)	Weight (kg.)		Serum *p*H (mEq./l.)		Serum HCO_3^- (mEq./l.)		Serum Cl^- (mEq./l.)		Serum Na^+ (mEq./l.)		Serum K^+ (mEq./l.)		BUN (mg./100 ml.)		K^E (mEq.)		B.P. (mm. Hg) Bef.	Mean B.P. (mm. Hg) Bef.	B.P. (mm. Hg) Aft.	Mean B.P. (mm. Hg) Aft.
				Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Ref.	Aft.				
T.D.	69	F	170	71.4	69.3	7.41	7.48	26.4	27.2	106	102	140	140	4.60	4.69	15	22	3129	2250	184/104	131	150/110	123
L.C.	57	F	165	73.4	71.5	7.35	7.62	27.0	31.9	102	96	148	143	4.70	5.00	25	27	2514	2321	284/150	195	240/135	170
E.K.	36	M	145	62.4	61.7	7.37	7.32	28.7	28.8	106	100	149	145	4.50	4.04	14	10	3284	3227	160/100	120	160/120	133
J.B.	67	F	132	54.2	54.1	7.35	7.58	25.8	30.9	107	101	149	143	4.36	4.36	13	14	2253	1769	212/132	159	210/135	160
W.T.	40	M	179	75.0	75.2	7.41	7.36	27.2	25.8	98	100	135	140	5.13	4.72	22	8	4086	4200	138/98	111	138/80	99
M.C.	32	F	153	46.7	45.7	7.31	7.30	23.8	24.0	105	99	140	145	4.68	4.25	14	11	1758	1822	170/112	131	130/90	103
R.H.	59	M	168	69.4	68.9	7.35	7.37	27.3	29.2	104	103	138	144	3.65	3.92	19	19	2754	2657	160/100	120	130/100	110
A.F.	53	M	178	67.1	66.6	7.37	7.30	32.0	31.2	102	98	143	144	4.30	4.30	32	23	2820	4160	210/105	140	200/105	137
S.P.	53	M	178	90.5	89.2	7.33	7.23	28.6	27.8	104	97	136	138	4.03	4.10	21	20	3169	3704	222/124	157	265/160	195
B.R.	55	F	159	74.4	73.6	7.33	7.45	28.4	29.9	106	98	145	145	4.05	3.40	14	29			205/110	142	175/100	125
Mean				68.5	67.6	7.36	7.40	27.5	28.7	104	99	142	143	4.40	4.28	19	18	2863	2901		141		136
S.D.				12.1	11.9	0.03	0.13	2.2	2.5	3	2	5	3	0.42	0.46	6	7	668	955		25		31

* Daily dose: hydrochlorothiazide 100 mg., potassium chloride 0.6 gm.; Bef., before treatment; Aft., after treatment.

Table 5

Observations on 10 Patients with Hypertensive Heart Disease and No Edema, Following Administration of Hydrochlorothiazide together with Potassium Chloride for 28 Days*

Pat't	Age (yr.)	Sex	Ht. (cm.)	Weight (kg.)		Serum pH (mEq./l.)		Serum HCO_3^- (mEq./l.)		Serum Cl^- (mEq./l.)		Serum Na^+ (mEq./l.)		Serum K^+ (mEq./l.)		BUN (mg./100 ml.)		K^E (mEq.)		B.P. (mm. Hg) Bef.	Mean B.P. (mm. Hg) Bef.	B.P. (mm. Hg) Bef.	Mean B.P. (mm. Hg) Aft.
				Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.				
C.R.	59	F	170	63.5	62.4	7.29	7.33	23.9	29.0	103	100	139	142	4.83	4.87	16	19	1965	1922	188/108	135	150/90	110
A.W.	59	F	166	73.4	72.5	7.35	7.45	28.1	31.5	103	100	137	142	3.50	4.47	15	21	2242	3612	220/140	166	150/110	123
J.S.	65	M	166	85.0	84.5	7.37	7.35	26.6	26.0	102	99	135	139	4.00	4.05	27	19	3126	3058	150/90	110	150/95	113
O.H.	54	F	156	74.8	73.2	7.49	7.41	22.0	34.1	101	95	131	136	5.00	3.53	18	33	2212	2106	200/120	147	190/110	137
C.S.	46	F	156	82.6	80.2	7.32	7.47	31.2	32.6	104	102	137	148	4.62	3.98	24	43	2584	2317	185/125	145	190/110	137
I.L.	52	F	157	101.5	101.8	7.41	7.41	27.6	29.4	105	104	145	138	4.80	4.80	20	19	2866	2350	180/115	137	190/110	137
E.G.	45	F	163	70.9	70.6	7.37	7.43	26.1	25.0	106	105	142	139	4.80	4.57	13	14	2575	2308	220/130	160	210/115	147
A.Mc.	47	F	153	100.0	102.8	7.31	7.36	24.8	27.4	106	101	145	140	5.00	4.75	21	24	2559	2503	200/100	133	180/110	133
J.W.	51	F	166	97.8	98.2	7.33	7.37	26.5	29.5	106	103	145	137	4.50	4.30	19	21	2571	2406	190/125	147	200/120	147
J.McD.	53	F	168	60.1	60.9	7.33	7.38	27.9	27.4	106	107	147	140	4.55	4.10	12	11	2639	2316	220/70	120	170/100	123
Mean				81.0	80.7	7.36	7.40	26.5	29.2	104	102	140	140	4.56	4.34	19	22	2534	2490		140		131
S.D.				15.0	15.7	0.06	0.05	2.5	2.9	2	3	5	3	0.47	0.43	5	9	355	491		17		11

* Daily dose: hydrochlorothiazide 50 mg., potassium chloride 0.6 gm.; Bef., before treatment; Aft., after treatment.

TABLE 6

OBSERVATIONS ON 14 PATIENTS WITH HYPERTENSIVE HEART DISEASE AND NO EDEMA, FOLLOWING ADMINISTRATION OF HYDROCHLOROTHIAZIDE TOGETHER WITH AMMONIUM CHLORIDE FOR 28 DAYS*

Pat't	Age (yr.)	Sex	Ht. (cm.)	Weight (kg.)		Serum pH (mEq./l.)		Serum HCO_3^- (mEq./l.)		Serum Cl^- (mEq./l.)		Serum Na^+ (mEq./l.)		Serum K^+ (mEq./l.)		BUN (mg./100 ml.)		K^E (mEq.)		B.P. (mm. Hg) Bef.	Mean B.P. (mm. Hg) Bef.	B.P. (mm. Hg) Aft.	Mean B.P. (mm. Hg) Aft.
				Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.	Bef.	Aft.				
N.C.	41	F	160	79.7	78.4	7.49	7.29	29.0	23.7	102	105	135	137	4.60	5.05	16	24	2664	2588	200/115	143	165/100	122
V.J.	54	F	158	74.7	74.1	7.45	7.54	25.3	26.1	105	106	141	140	4.86	3.88	18	12	2131	2390	225/110	148	220/105	143
E.C.	43	M	170	77.8	79.7	7.39	7.44	31.5	33.3	89	96	138	140	4.07	3.99	19	16	2857	2835	140/98	112	145/95	112
M.B.	53	F	160	86.8	85.1	7.34	7.31	26.0	25.4	103	100	136	138	4.00	4.02	9	10	2313	2340	230/125	160	180/100	127
L.D.	43	M	178	92.8	90.2	7.33	7.41	31.7	32.8	99	98	137	137	3.90	3.55	17	24	3241	3287	175/135	148	160/115	130
B.N.	56	F	155	81.0	77.6	7.36	7.33	28.1	26.4	107	100	131	139	3.36	3.52	13	25	2005	1812	170/100	123	190/115	140
J.H.	60	F	158	54.1	53.9	7.45	7.35	25.1	22.8	104	107	127	140	4.17	4.67	20	27	1723	1846	182/100	127	155/95	115
E.B.	58	F	158	55.9	55.1	7.35	7.37	27.8	26.1	103	104	137	133	4.68	4.65	17	12	2046	2107	216/120	152	205/115	145
K.D.	62	F	150	66.6	64.9	7.36	7.40	27.3	30.1	103	99	136	137	4.36	3.83	4	14	1845	1733	190/108	135	220/110	147
W.H.	37	M	175	90.7	85.1	7.35	7.45	28.0	27.0	105	101	135	148	4.60	4.03	10	11	3581	3894	150/120	130	145/100	115
W.A.	40	M	165	110.0	111.9	7.30	7.45	24.8	27.1	109	102	144	138	4.76	5.69	12	21	3669	3797	164/96	119	150/100	117
I.M.	37	F	153	57.3	56.8	7.46	7.35	23.7	23.5	105	107	137	136	3.90	4.54	3	11	2005	2025	195/110	138	180/130	147
I.F.	57	F	165	70.1	69.2	7.37	7.33	25.9	25.7	105	106	131	138	4.85	5.52	14	22	2239	2179	170/80	110	130/60	83
L.L.	49	F	155	70.2	68.0	7.40	7.39	27.0	27.1	104	98	136	134	4.43	4.72	8	17	2884	2600	200/110	140	150/80	103
Mean				76.3	75.0	7.39	7.39	27.2	26.9	103	102	136	138	4.32	4.40	13	18	2515	2531		135		125
S.D.				15.7	15.7	0.06	0.07	2.4	3.2	5	4	4	4	0.44	0.69	5	6	642	700		15		19

* Daily dose: hydrochlorothiazide 100 mg., ammonium chloride 1.0 gm.; Bef., before treatment; Aft., after treatment.

TABLE 7

STATISTICAL SUMMARY OF DATA FROM TABLES 2 THROUGH 6

Variable measured	Hydrochlorothiazide 100 mg./day			Benzydroflumethiazide 10 mg./day			Hydrochlorothiazide 100 mg. plus KCl 0.6 gm. daily			Hydrochlorothiazide 50 mg. plus KCl 0.6 gm. daily			Hydrochlorothiazide 100 mg. plus NH₄Cl 1.0 gm. daily		
	Initial	Δ	P	Initial	Δ	P	Initial	Δ	P	Initial	Δ	P	Initial	Δ	P
Weight (kg.)	73.5	−1.1	N.S.	76.3	−0.8	N.S.	68.5	−0.9	N.S.	81.0	−0.3	N.S.	76.3	−1.3	N.S.
*p*H (mEq./l.)	7.33	+0.07	<0.001	7.37	+0.05	<0.001	7.36	+0.04	N.S.	7.36	+0.04	N.S.	7.39	0	N.S.
HCO_3^- (mEq./l.)	27.1	+3.3	<0.001	26.4	+1.9	<0.025	27.5	+1.2	N.S.	26.5	+2.7	<0.05	27.2	−0.3	N.S.
Cl^- (mEq./l.)	102	−6	<0.001	105	−4	<0.001	104	−5	<0.001	104	−2	N.S.	103	−1	N.S.
Na^+ (mEq./l.)	141	+2	N.S.	137	0	N.S.	142	+1	N.S.	140	0	N.S.	136	+2	N.S.
K^+ (mEq./l.)	4.42	−0.60	<0.001	4.46	−0.59	<0.001	4.40	−0.12	N.S.	4.56	−0.22	N.S.	4.32	+0.08	N.S.
BUN (mg./100 ml.)	16	+3	N.S.	15	+1	N.S.	19	−1	N.S.	19	+3	N.S.	13	+5	<0.025
K^E (mEq.)	2695	+48	N.S.	2550	+4	N.S.	2863	+38	N.S.	2534	−44	N.S.	2515	+16	N.S.
M.B.P. (mm. Hg)	151	−19	<0.001	135	−1	N.S.	141	−5	N.S.	140	−9	N.S.	135	−10	N.S.

TABLE 8

OBSERVATIONS ON 9 PATIENTS WITH HYPERTENSIVE HEART DISEASE AND NO EDEMA, FOLLOWING TREATMENT WITH HYDROCHLOROTHIAZIDE* FOR 14 DAYS

Pat't	Age (yr.)	Sex	Ht. (cm.)	Weight (kg.)				Serum *p*H				Serum HCO_3^-				Serum Cl^-				Serum Na^+				Serum K^+				BUN				K^E		M. B. P.			
				1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	1	2	3	4
B.N.	56	F	155	77.6	75.9	76.0	75.9	7.34	7.39	7.43	7.47	28.1	29.3	29.4	29.7	107	98	99	99	131	133	140	148	3.36	3.29	3.37	2.93	13	22	21	16	1812	1811	127	137	142	138
J.H.	60	F	158	54.4	54.1	54.1	54.9	7.35	7.49	7.47	7.44	25.1	23.6	26.1	23.7	104	105	104	105	127	135	139	145	4.17	4.20	4.68	4.04	20	36	30	32	1846	1968	102	117	107	109
W.H.	37	M	175	50.6	78.1	80.1	79.5	7.36	7.41	7.49	7.40	28.0	28.3	26.8	28.1	105	101	105	109	135	142	140	145	4.60	3.50	4.10	3.76	10	12	11	17	3613	3612	120	118	120	120
E.B.	58	F	158	53.8	52.7	50.6	50.8	7.33	7.39	7.59	7.37	27.8	26.5	32.6	30.4	103	104	94	96	137	133	136	146	4.68	3.74	3.00	3.05	17	13	17	17	2046	1708	120	150	127	122
K.D.	62	F	150	65.7	64.9	64.8	66.1	7.35	7.39	7.39	7.45	27.3	28.2	26.4	30.3	103	98	101	101	136	132	139	149	4.36	3.48	4.38	4.34	4	10	15	13	1845	1828	143	130	137	133
W.A.	40	M	165	114.1	116.7	115	113.6	7.33	7.39	7.41	7.40	24.8	29.7	30.1	28.7	109	101	99	100	144	137	136	136	4.76	4.27	3.33	4.43	12	9	17	17	3661	3662	127	143	153	133
I.F.	57	F	165	67.3	67.3	67.6	68.2	7.34	7.37	7.51	7.42	25.9	27.1	27.2	28.3	105	97	101	100	131	134	133	136	4.85	3.95	4.22	4.37	14	22	15	15	2165	2111	130	120	135	110
E.H.	34	F	156	94.4	92.4	91.6	93.6	7.36	7.38	7.39	7.44	28.2	31.4	33.3	29.1	99	93	90	101	140	133	133	137	4.80	3.28	2.53	4.64	13	14	19	15	2151	1881	120	137	123	135
I.M.	37	F	153	56.5	55.7	58.1	57.7	7.35	7.42	7.49	7.46	23.7	27.2	23.8	26.1	105	99	107	105	137	134	134	133	3.90	2.62	2.82	3.22	3	9	6	6	1977	1904	123	107	150	140
Mean				73.8	73.1	73.1	73.4	7.35	7.40	7.44	7.43	26.5	28.0	28.4	28.3	104	100	100	102	135	135	137	142	4.39	3.59	3.60	3.86	12	16	17	16	2346	2276	124	129	133	127
S.D.				20.3	20.9	20.5	20.1	.01	.04	.05	.03	2.3	2.2	3.2	2.2	3	4	5	4	5	3	3	6	0.50	0.52	0.76	0.65	6	9	7	7	743	780	11	14	15	12

* 1–2, 100 mg. daily; 2–3, 100 mg. daily plus NaCl 2.7 gm. daily; 3–4, 100 mg. daily plus NaCl 4.5 gm. daily.

TABLE 9
STATISTICAL SUMMARY OF DATA FROM TABLE 8

Variable measured	Hydrochlorothiazide 100 mg./day			Hydrochlorothiazide 100 mg. plus NaCl 2.7 gm./day				Hydrochlorothiazide 100 mg. plus NaCl 4.5 gm./day			
	Initial	Δ	P	Δ 1–3	P	Δ 2–3	P	Δ 1–4	P	Δ 3–4	P
Weight (kg.)	73.8	−0.7	N.S.	−0.7	N.S.	0	N.S.	−0.4	N.S.	+0.3	N.S.
*p*H	7.35	+0.05	<0.005	+0.09	<0.001	+0.04	N.S.	+0.08	<0.001	−0.01	N.S.
HCO_3^- (mEq./l.)	26.5	+1.5	N.S.	+1.9	N.S.	+0.4	N.S.	+1.8	N.S.	−0.1	N.S.
Cl^- (mEq./l.)	104	−4	<0.025	−4	N.S.	0	N.S.	−2	N.S.	+2	N.S.
Na^+ (mEq./l.)	135	0	N.S.	+2	N.S.	+2	N.S.	+7	<0.025	+5	<0.05
K^+ (mEq./l.)	4.39	−0.80	<0.005	−0.79	<0.025	+0.01	N.S.	−0.53	N.S.	+0.26	N.S.
BUN (mg./100 ml.)	12	+4	N.S.	+5	N.S.	+1	N.S.	+4	N.S.	−1	N.S.
M.B.P. (mm. Hg)	124	+5	N.S.	+9	N.S.	+4	N.S.	+3	N.S.	−6	N.S.
K^E (mEq.)	2346							−70	N.S.		

minor variations in weight occurred in each of the groups studied, none of these weight changes were statistically significant and there were no significant differences between the various programs of therapy.

Serum pH. The mean value for serum *p*H increased significantly in the groups of patients treated with hydrochlorothiazide or with benzydroflumethiazide alone ($P < 0.001$). When potassium chloride in a daily dose of 0.6 gm. was administered in combination with hydrochlorothiazide in a daily dose of 100 or 50 mg., a slight increase in the mean value for *p*H occurred, but this increase was not statistically significant. In the group of patients receiving 100 mg. hydrochlorothiazide, together with 1.0 gm. ammonium chloride daily, no change in the mean value for *p*H occurred. The daily administration of supplementary sodium chloride in doses of 2.7 and 4.5 gm. in combination with

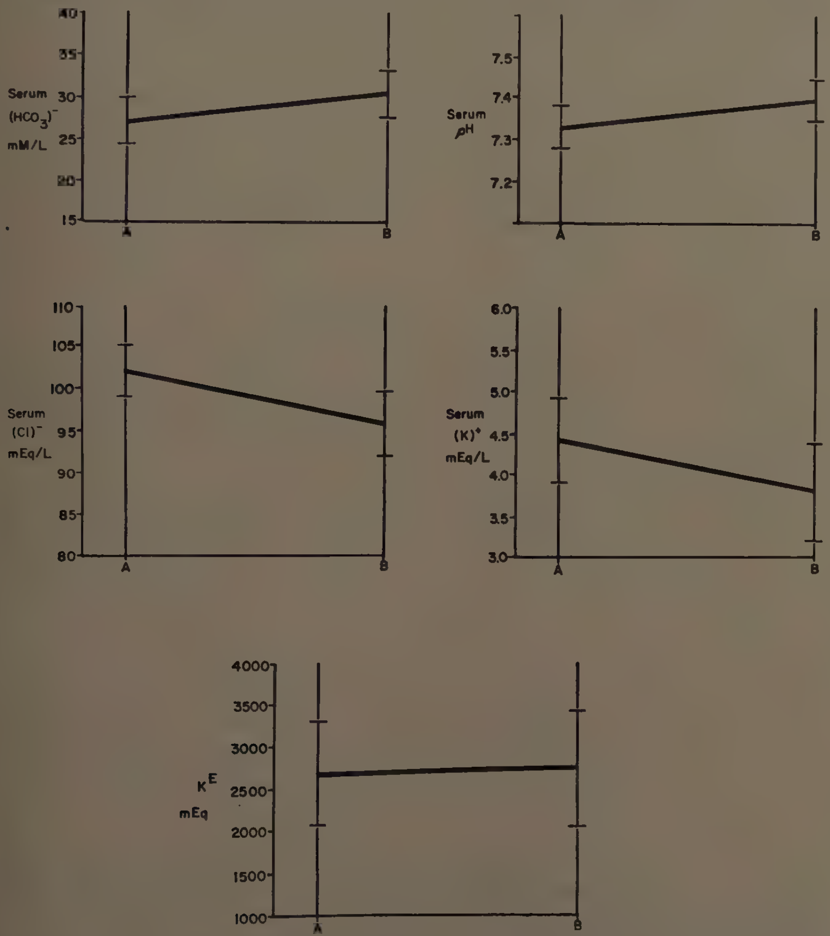

FIGURE 1. Effects of hydrochlorothiazide, 100 mg. daily, on the mean serum $(HCO_3)^-$, serum *p*H, serum $(Cl)^-$, serum $(K)^+$, and exchangeable potassium (K^E). The horizontal lines represent the standard deviations.

100 mg. of hydrochlorothiazide did not significantly alter the anticipated increase in pH that occurs with hydrochlorothiazide alone.

Serum bicarbonate. A statistically significant increase in serum bicarbonate concentration occurred in the groups of patients receiving either hydrochlorothiazide or benzydroflumethiazide alone ($P < 0.001$). When potassium chloride in a dose of 0.6 gm. was administered in combination with hydrochlorothiazide in a daily dose of 100 mg., the change in mean serum bicarbonate concentration was not significant. However, when 0.6 gm. potassium chloride was administered with 50 mg. hydrochlorothiazide, the change in serum bicarbonate was significant at the 5 per cent level ($P < 0.05$). Ammonium chloride in combination with hydrochlorothiazide caused a slight but statistically insignificant decrease in the mean serum bicarbonate concentration. In the group that received supplements of sodium chloride, no significant changes in the mean serum bicarbonate concentration were observed.

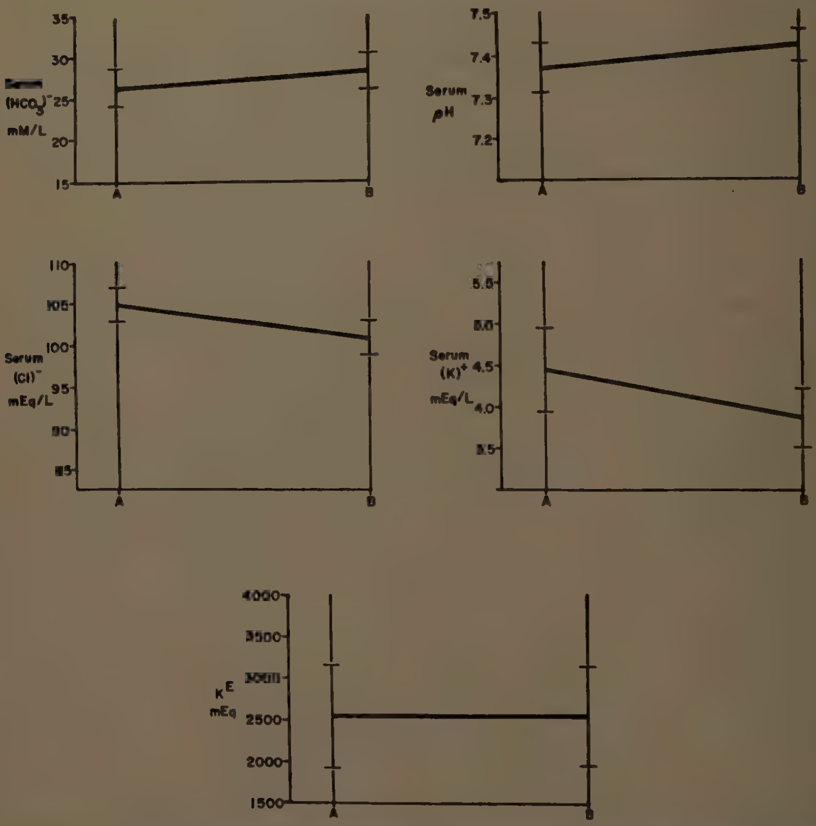

FIGURE 2. Effects of benzydroflumethiazide, 10 mg. daily on the mean serum $(HCO_3)^-$, serum pH, serum $(Cl)^-$, serum $(K)^+$, and exchangeable potassium (K^E). The horizontal lines represent the standard deviations.

Serum chloride. The mean value for serum chloride decreased significantly in the patients receiving hydrochlorothiazide or benzydroflumethiazide alone ($P < 0.001$). In the group of patients receiving 100 mg. hydrochlorthiazide together with 0.6 gm. potassium chloride daily, a significant decrease in the mean serum chloride concentration also was noted ($P < 0.001$). No significant changes in the mean value for serum chloride were observed in the group receiving 50 mg. hydrochlorothiazide with KCl 0.6 gm. potassium chloride daily or in the group receiving 100 mg. hydrochlorothiazide together with 1.0 gm. ammonium chloride daily. In the group of patients that received supplementary sodium chloride, an initial decrease in serum chloride was observed during the period that hydrochlorothiazide was administered alone ($P < 0.025$). With the addition of supplementary sodium chloride in daily doses of 2.7 and 4.5 gm., the mean value for serum chloride increased slightly and thus modified the hypochloremic effects of hydrochlorothiazide administration.

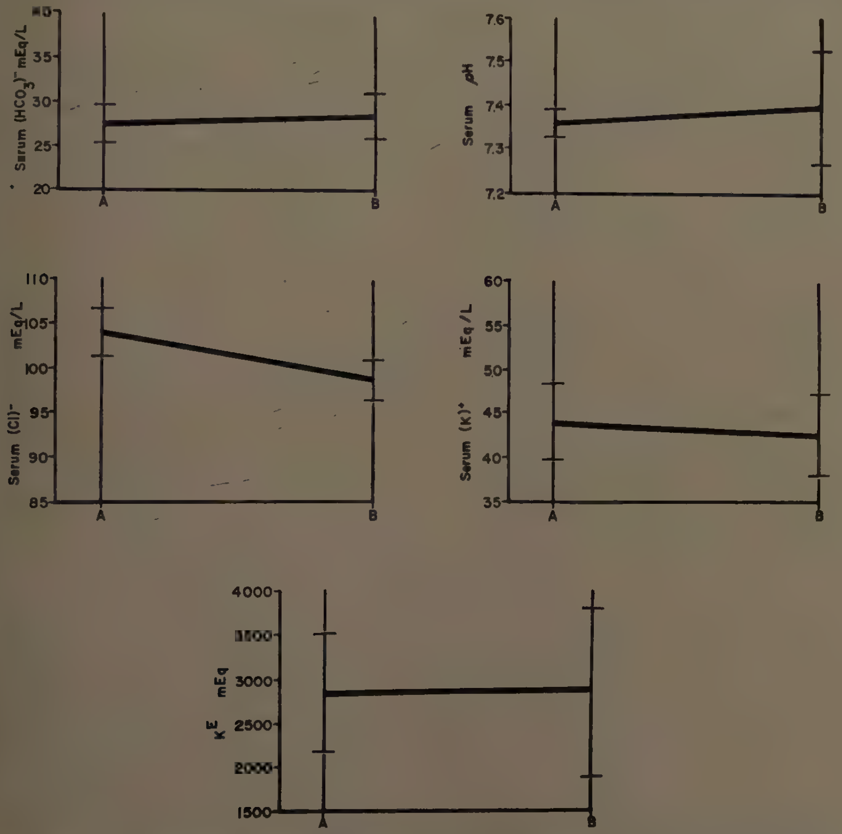

FIGURE 3. Effects of hydrochlorothiazide, 100 mg., together with 0.6 gm. daily potassium chloride on the mean serum $(HCO_3)^-$, serum pH, serum $(Cl)^-$, serum $(K)^+$, and exchangeable potassium (K^E). The horizontal lines represent the standard deviations.

Serum sodium. Slight changes in serum sodium concentration were observed in each group of patients studied; however, these changes were not statistically significant except in the group of patients receiving supplementary sodium chloride. In these patients, a significant rise in the mean serum sodium concentration was noted when the daily dose of supplementary sodium chloride was raised to 4.5 gm. ($P < 0.025$).

Serum potassium. Significant decreases in the mean serum potassium concentration were observed in the groups receiving hydrochlorothiazide or benzydroflumethiazide alone ($P < 0.001$). Slight but statistically insignificant decreases in serum potassium concentration were noted in the patient groups receiving 100 mg. hydrochlorothiazide together with 0.6 gm. of potassium chloride and 50 mg. hydrochlorothiazide together with 0.6 gm. of potassium chloride daily. In the group of patients receiving 100 mg. hydrochlorothiazide together with 1.0 gm. ammonium chloride daily the mean value for serum potassium actually increased slightly; however, this increase was not statistically significant. In the group receiving supplements of sodium chloride a statistically significant decrease in the mean serum potassium occurred during the

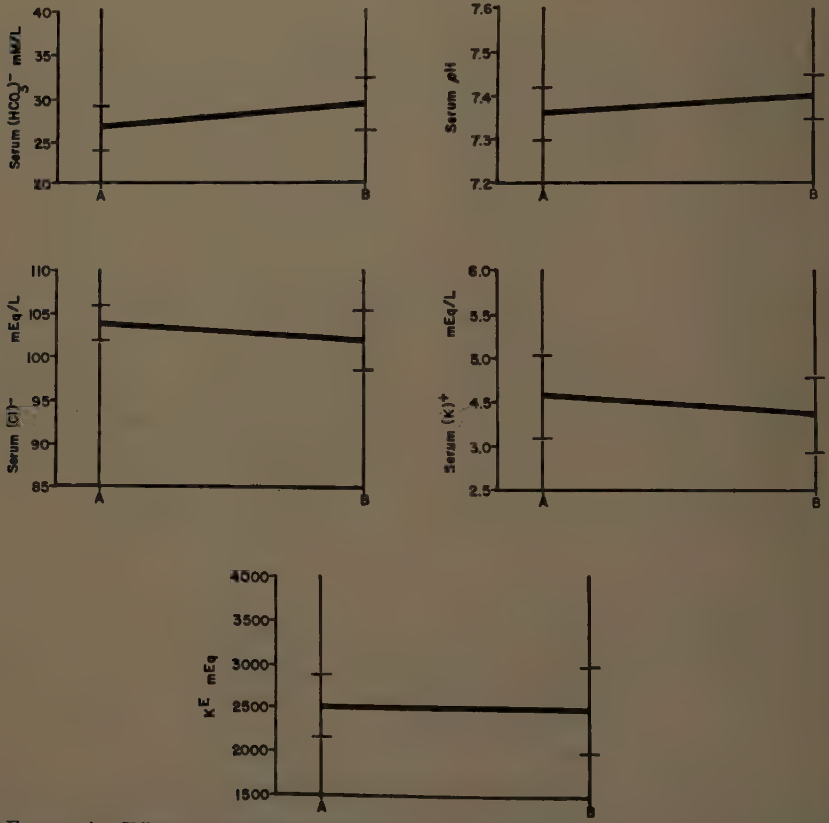

FIGURE 4. Effects of hydrochlorothiazide, 50 mg., together with 0.6 gm. daily potassium chloride on the mean serum $(HCO_3)^-$, serum *p*H, serum $(Cl)^-$, serum $(K)^+$, and exchangeable potassium (K^E). The horizontal lines represent the standard deviations.

two-week period that hydrochlorothiazide alone was administered ($P < 0.005$). With the addition of 2.7 gm. supplementary sodium chloride a slight rise in the mean value for serum potassium was noted, but this value still was significantly lower than the control value ($P < 0.025$). When the dose of supplementary sodium chloride was raised to 4.5 gm. daily, the mean value for serum potassium increased further and, although it remained below the control value, the difference between this final value and the control value was not significant.

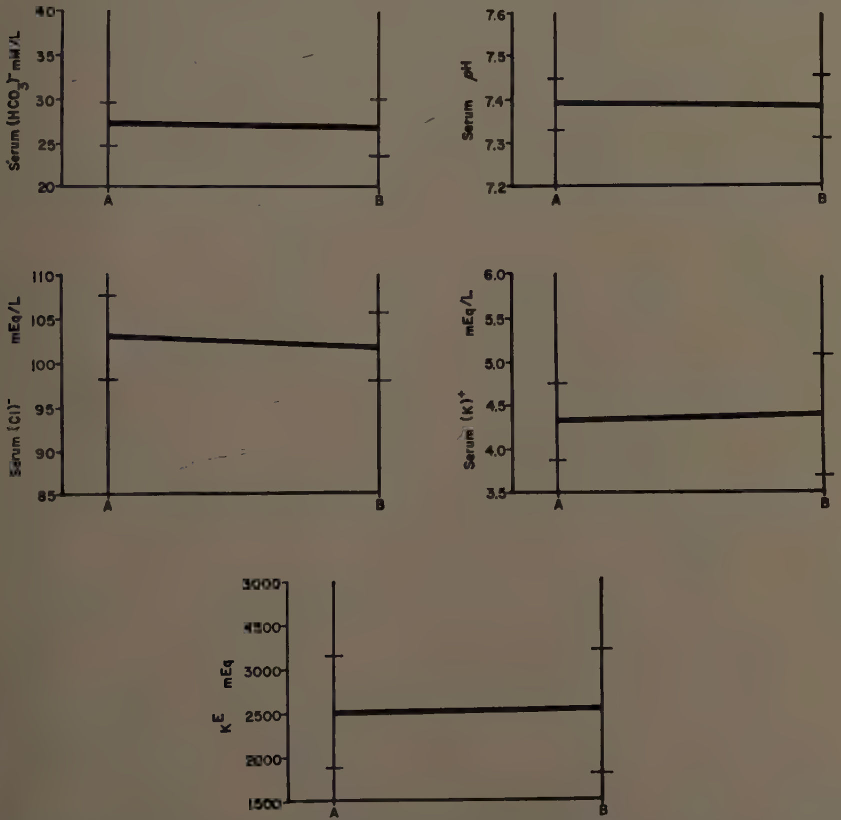

FIGURE 5. Effects of hydrochlorothiazide, 100 mg., together with 1.0 gm. daily ammonium chloride on the mean serum $(HCO_3)^-$, serum *p*H, serum $(Cl)^-$, serum $(K)^+$, and exchangeable potassium (K^E). The horizontal lines represent the standard deviations.

Blood urea nitrogen. Slight increases in the mean value for the blood urea nitrogen occurred in all groups except the one receiving 100 mg. hydrochlorothiazide daily together with 0.6 gm. potassium chloride. The increase in blood urea nitrogen, however, was not significant, except in the group receiving hydrochlorothiazide together with ammonium chloride ($P < 0.025$).

Exchangeable potassium. Small changes in the value for exchangeable potassium occurred in all of the groups studied; however, these changes were not statistically significant in any of the groups.

Mean blood pressure. Small changes in the mean blood pressure were noted in the various groups studied; however, a significant decrease in mean blood pressure was observed only in the group receiving 100 mg. hydrochlorothiazide alone daily.

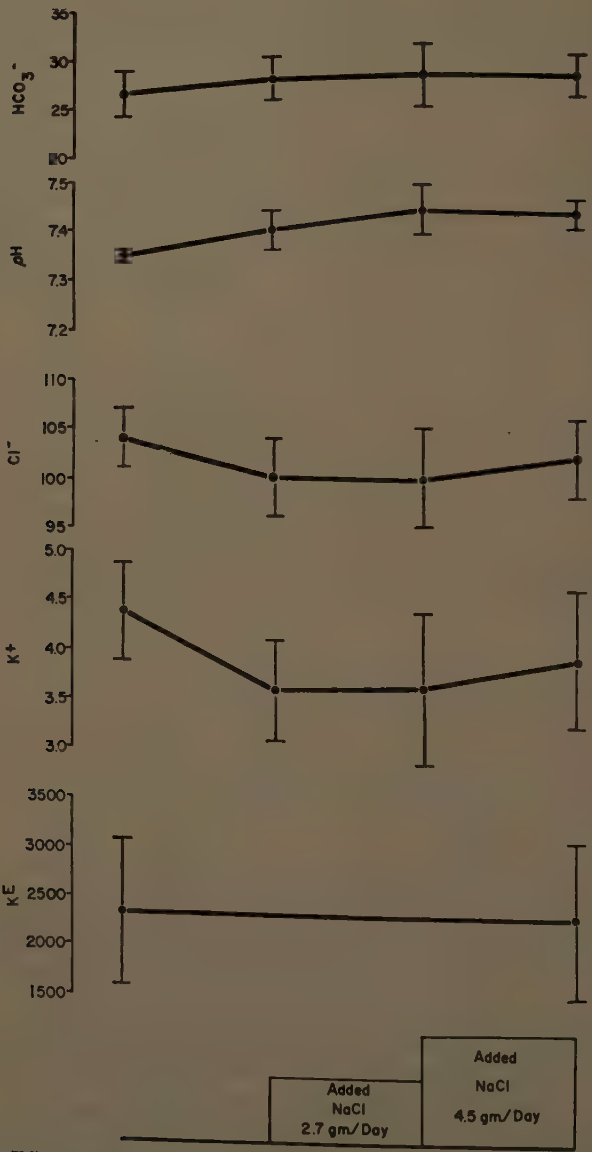

FIGURE 6. Effects of hydrochlorothiazide, 100 mg. daily, and the effects of supplementary sodium chloride in doses of 2.7 and 4.5 gm. daily, on the mean serum $(HCO_3)^-$, serum pH, serum $(Cl)^-$, serum $(K)^+$, and exchangeable potassium (K^E). The horizontal lines represent the standard deviations.

Clinical. Complaints of muscular cramps or muscular weakness occurred in some of the patients, but these did not correlate well with the laboratory data. In the patients receiving hydrochlorothiazide alone, electrocardiographic changes compatible with hypokalemia were noted in only one patient (A.L., TABLE 2). These alterations included depression of the junction between the QRS and S-T segment, straightening of the S-T segment, and the appearance of a "U" wave.

Relationship between serum pH and serum potassium. To determine the relationship between the serum *p*H and the serum potassium concentration, the values for these measurements were plotted for the patients receiving hydrochlorothiazide and benzydroflumethiazide alone (FIGURE 7). The coefficient of correlation for these data was −0.48 (P < 0.001).

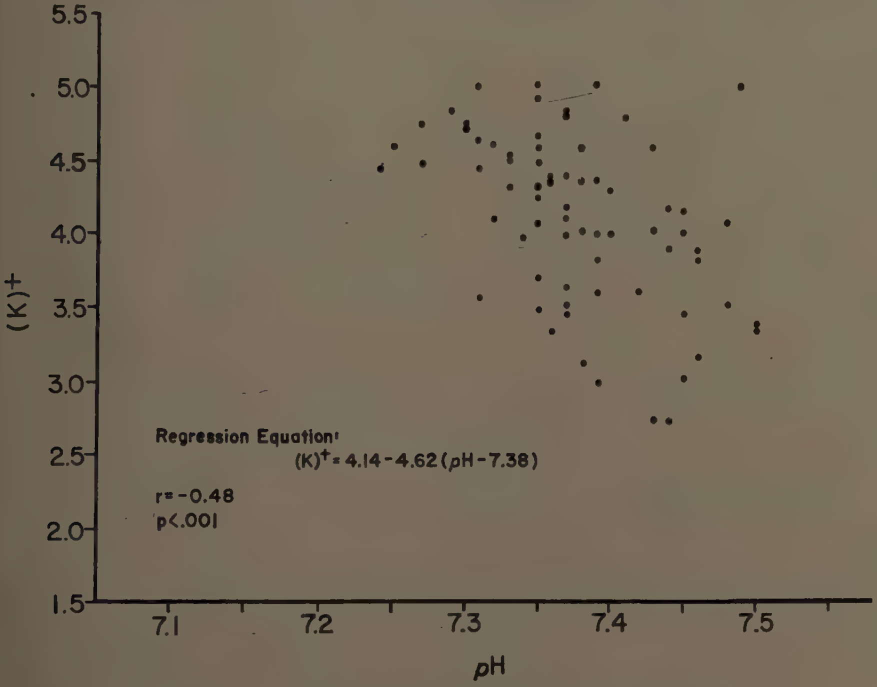

FIGURE 7. Relationship between serum potassium and *p*H.

Discussion

The growing popularity of the benzothiadiazine derivatives in the management of hypertensive disease and in the treatment of various edematous states has dictated an increased interest in the effects of these compounds on potassium metabolism. Early studies demonstrated that, in addition to the diuretic, chloruretic, and natriuretic properties exhibited by these compounds, significant kaluresis also occurred. Such studies generally were extended only for short periods of time and, as a result, when significant hypokalemia was observed during prolonged administration of these compounds, it was assumed that this reflected frank potassium depletion. Studies performed in our laboratory have demonstrated that, although a marked kaluresis occurs during the first several days of drug therapy, this kaluretic effect became less pronounced as therapy continued. Serial measurements of exchangeable potassium under such circumstances revealed that in many instances the value for exchangeable potassium decreased after one week of therapy with benzothiadiazine and then returned to pretreatment levels during continued administration of the drug. Despite this, the low values for serum potassium persisted. This suggested that the hypokalemia occurring with continued benzothiadiazine therapy results from a redistribution of potassium rather than from frank depletion. The interrelationship between alterations in extracellular *p*H and changes in serum potassium concentration have been documented by numerous investigators.[8-13] Since one of the metabolic effects of the benzothiadiazine derivatives is the production of a metabolic alkalosis with an increase in serum bicarbonate and in serum *p*H, it appeared to be of interest to evaluate the effects of administering supplementary electrolytes to patients receiving benzothiadiazine derivatives.

In the present study, supplementary potassium was supplied in a dose of 0.6 gm. daily, which represents 10 to 20 percent of the average daily intake of potassium (40 to 80 mEq.). The dose of ammonium chloride was arbitarily selected as one that would provide a continuing supply of hydrogen ions, but would not induce a significant potassium diuresis. The doses of supplementary sodium chloride were chosen because these quantities (2.7 and 4.5 gm. daily) represented significant increases in the estimated average daily sodium intake of our patient population, which approximates 3.0 gm. daily.

The results obtained in these studies indicate that, in the doses administered, electrolyte metabolism was favorably influenced by the administration of each of these supplements. The administration of potassium chloride appeared to limit the decrease in serum potassium concentration produced by the administration of benzothiadiazines alone, but it also modified the increases in serum bicarbonate and *p*H, suggesting that the effects of potassium supplementation act through mechanisms other than simply increasing the body's potassium stores. In the group of patients receiving ammonium chloride, the anticipated increase in serum bicarbonate and in *p*H, as well as the decrease in serum chloride concentration, was prevented. Simultaneously, hypokalemia did not occur, despite the fact that no supplementary potassium was provided. The administration of liberal supplements of sodium chloride failed to influence the anticipated changes in serum *p*H; however, an effect on the serum potassium concentration was observed, especially with a dosage of 4.5 gm. daily. It is important to note that the effects of the minute quantities of potassium chloride contained in the Thermotabs cannot be evaluated adequately from the current data.

In a recent report, Leibman and Edelman[13] have demonstrated that the plasma potassium concentration is related to the extracellular *p*H, body potassium content, and plasma sodium concentration, in decreasing order of importance. The results obtained in the current study are in keeping with the observations of these investigators. The coefficient of correlation between the serum *p*H and the serum potassium concentration obtained in the present studies is comparable to that reported by Leibman.

In the present studies, since total body potassium remained essentially unchanged, as measured by the isotope dilution technique, the level of serum potassium concentration appears to be influenced largely by the serum *p*H. Corrections for body potassium content and serum sodium concentration failed to improve the coefficient of correlation between the serum potassium concentration and the observed hydrogen ion concentration, thus suggesting that other factors, perhaps related to the effects of the hypertensive state or of the drug therapy on the permeability of the cellular membrane, play an additional role in determining the serum potassium concentration.

Summary and Conclusions

Lowering of serum potassium concentration of varying degrees has been shown to occur in approximately 85 per cent of patients receiving benzothiadiazines. In order to elucidate the mechanism by which this hypokalemia occurs, measurements of serum electrolytes and exchangeable potassium were performed before and after each of the following programs of therapy:

(1) Hydrochlorothiazide, 100 mg. daily for 28 days (20 patients).

(2) Benzydroflumethiazide, 10 mg. daily for 28 days (17 patients).

(3) Hydrochlorothiazide, 100 mg. plus potassium chloride 0.6 gm. daily for 28 days (10 patients).

(4) Hydrochlorothiazide, 50 mg. plus potassium chloride 0.6 gm. daily for 28 days (10 patients).

(5) Hydrochlorothiazide, 100 mg. plus ammonium chloride, 1.0 gm. daily for 28 days (14 patients).

(6) Hydrochlorothiazide, 100 mg. daily with supplementary rations of sodium chloride in doses of 2.7 and 4.5 gm. daily for 14 days each (9 patients).

The analysis of the data obtained revealed that the mean value for exchangeable potassium did not change significantly with any of the programs of treatment. With the administration of either hydrochlorothiazide alone or benzydroflumethiazide alone, a significant decrease in the mean serum potassium and chloride concentration accompanied a significant increase in serum *p*H and bicarbonate concentration. When supplements of potassium, ammonium, or sodium chloride were administered in conjunction with hydrochlorothiazide, the anticipated changes in electrolyte concentrations were beneficially modified. In this role, in the doses administered, ammonium chloride appeared to be the most effective and sodium chloride the least effective. The data suggest that alterations in extracellular hydrogen ion concentration exert a significant effect in producing hypokalemia during benzothiadiazine administration, but that other factors relating to the hypertensive state or to the medication also are involved.

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CLINICAL EXPERIENCES WITH SOME OF THE NEWER DIURETICS, ESPECIALLY CHLORTHALIDONE

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This paper presents a clinical and metabolic study of new diuretics, particularly chlorthalidone,* in relation to normal subjects and patients with edema.

After observing the effect on sodium and potassium excretion of five normal subjects, we studied the diuretic in cardiac and cirrhotic patients who had been treated previously with a strict salt-free diet, cardiotonic agents, and other diuretics.

Since it is difficult to evaluate the effect of a diuretic upon patients in whom the conditions of diuresis vary from one phase of the illness to another, we attempted to determine precisely the situations that prevent diuretic action. We were thus led to conclude that there were periods during which the excretion of sodium was greatly reduced and the aldosterone excretion greatly increased, periods during which the patient was resistant to treatment with diuretics.

When the patient was unable to excrete sodium, it was sometimes possible to obtain the desired effect with certain diuretics by combining them with prednisone or spirolactone treatment.

For the conclusion of this investigation we studied two undesirable effects associated with the use of diuretics: the excretion of potassium, causing hypokalemia when not compensated by a sufficient supply; and changes in blood coagulation, which we were able to demonstrate by changes in the thrombelastogram.

Materials and Methods

Our experiment was carried out with 5 normal subjects who were placed on a strict salt-free diet for several days, with administration of a fixed quantity of 5 or 9 gm. of NaCl every 24 hours, and 120 cardiac or cirrhotic cases during the period of water and salt retention. The majority of the patients were kept on a strict salt-free diet for a certain length of time and received, with or without success, other diuretics. Several of them were observed at different stages of their disease, during the period of moderate retention and during the period of almost complete retention of sodium, with and without increased urinary aldosterone excretion and under hemodynamic conditions that were stable or modified by phlebotomy, paracentesis, or modification of the cardiac rhythm.

Chlorthalidone was administered in a single dose varying from 25 to 200 mg. among normal subjects and up to 600 mg. for patients with edema. In several cases we gave 200 mg. every 24 hours for 4 days.

The diuretic effect of the medication was evaluated by balance studies with measurement of sodium administered and of the urinary elimination of water, sodium, chloride, and potassium.

In 5 normal subjects and 1 cardiac case with edema, the urinary excretion of sodium and potassium was measured every 3 hours for 24 hours before and 48 hours after administration of the medication.

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* Hygroton, G 33182 (3-hydroxy-3-[4-chloro-3-sulfamylphenyl] phthalimidine), supplied by Geigy Chemical Corporation, Ardsley, N. Y.

One normal subject, who received 4 gm./day of NaCl, was studied over a 24-hour period for the effects of increasing doses successively administered at intervals of several days.

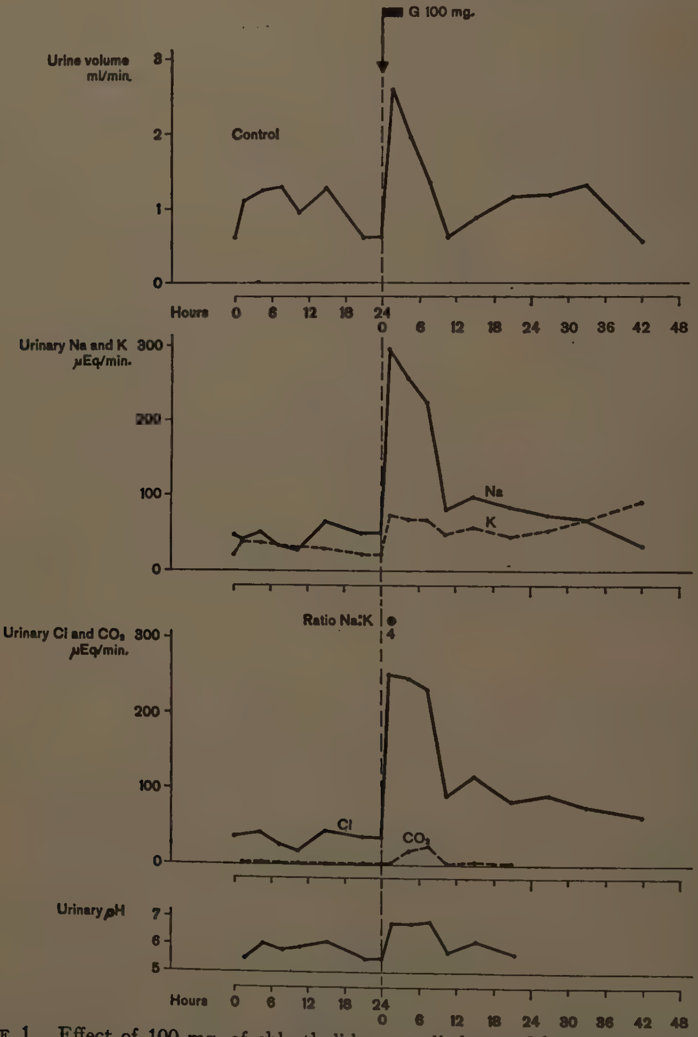

FIGURE 1. Effect of 100 mg. of chlorthalidone studied over 3-hour periods in a normal patient, G.C., a male 55 years old. Subject observed a strict salt-free diet, but 6 gm. of NaCl were administered each day.

Repeated determinations of urinary aldosterone were carried out in many patients by the Neher-Wettstein method.[1] Several determinations of aldosterone secretion were carried out by the Peterson method (Muller *et al.*[2]).

Thrombelastogram patterns were recorded according to Harter in normal subjects dehydrated by a strict salt-free diet, and in patients with water retention in spite of a salt-free diet and administration of diuretics.

Conditions of nonresponse to diuretics were evaluated by using various diuretics and extensive balance determinations.

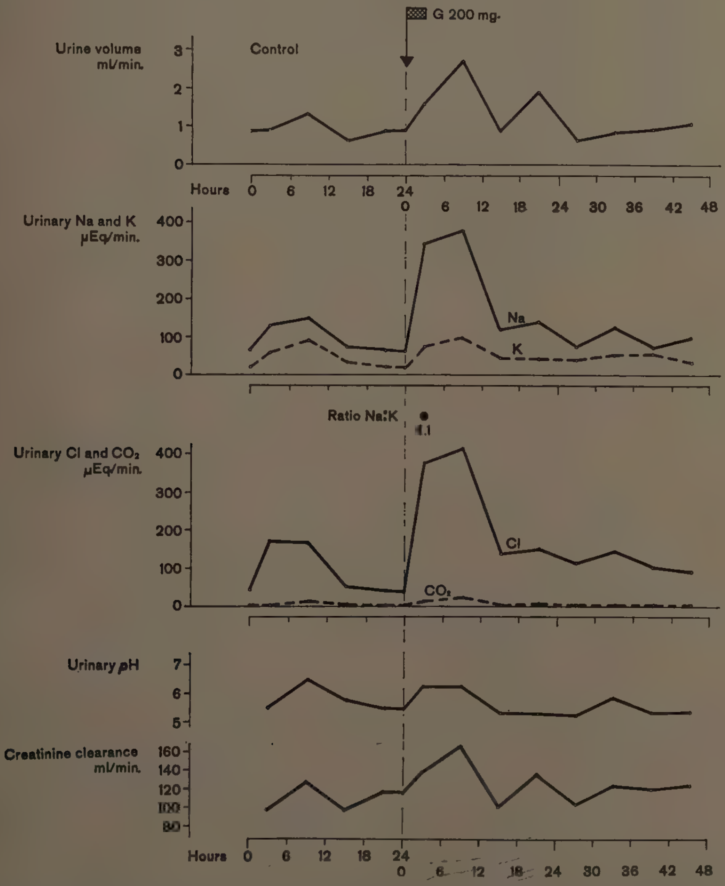

FIGURE 2. Effect of 200 mg. of chlorthalidone studied over 3-hour periods in a normal patient, E.K., a male 36 years old. Subject observed a strict salt-free diet, but 9 gm. of NaCl were administered each day.

Results

Effect of chlorthalidone on normal subjects. FIGURES 1 and 2 show the effect of a single dose of 100 mg. or 200 mg. in normal subjects. In the hours following administration of the compound, diuresis increases from 1 ml. to 2.5 ml./min., while urinary sodium excretion increases from 200 μEq. to 250 μEq./min. Sodium excretion reaches its maximum within the first 9 hours and remains increased for another 9 hours. This prolonged natriuretic action is one of the characteristic properties of the drug. It is even more marked in patients with severe salt retention.

Potassium loss, varying from 40 to 75 μEq./min., also persists longer than the first day.

Increased urinary CO_2 elimination, a moderate increase in urinary pH that does not reach the neutral point, and a slight decrease in titrable acidity, as well as in urinary ammonium, is also observed. This carbonic anhydrase inhibiting effect is quantitatively insignificant and much less than that of acetazolamide.

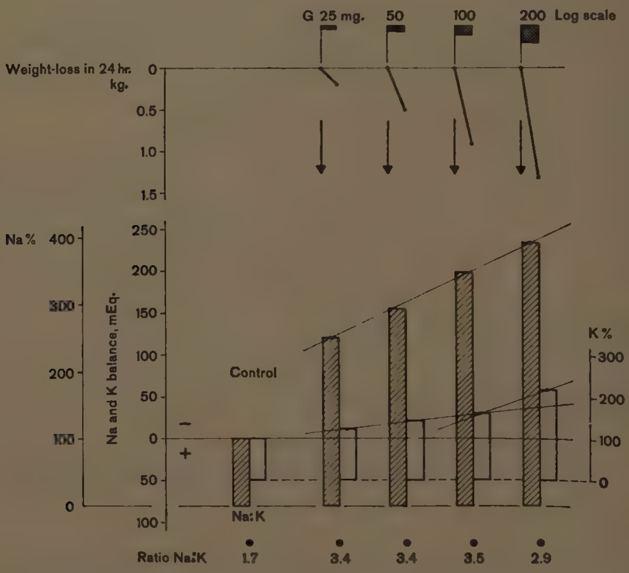

FIGURE 3. Excretion of sodium and potassium in the urine over a 24-hour period under the influence of increasing doses of chlorthalidone. Subject was a normal male, M.P., 25 years old, who observed a strict salt-free diet with the addition of 4 gm. of NaCl each day.

Endogenous creatinine clearance is somewhat increased during the first 12 hours when the diuresis is most massive.

The normal subject exhibited a relationship between the dose of the diuretic administered and the natriuretic effect produced by doses within the therapeutic range (FIGURE 3). Thus a young man receiving 80 mEq. of sodium every 24 hours exhibited an increase in urinary sodium of 115 mEq. for a single dose of 25 mg. chlorthalidone, 150 mEq. for a dose of 50 mg., 200 mEq. for a dose of 100 mg. and 230 mEq. for a dose of 200 mg. every 24 hours. The urinary sodium increased linearly for a logarithmic increase of the medication dosage.

The dose of 200 mg. chlorthalidone also increased the excretion of urinary potassium, which was depleted by more than 50 mEq. a day.

The effect of chlorthalidone upon cardiac and cirrhotic patients with water re-

tention. FIGURE 4 shows the marked diuresis produced by a single dose of 400 mg. chlorthalidone in a hyperthyroid female, 52 years of age, with cardiac insufficiency and auricular fibrillation. The 6.7 l. of urine excreted in the first day contained 917 mEq. sodium and 128 mEq. potassium. Particularly remarkable was that this enormous diuresis did not result in a rebound phenomenon on the following day; on the contrary, the diuretic action was extended, and for a period of 3 days produced elimination of 1600 mEq. of sodium and 280 mEq. of potassium. The total weight loss was 12 kg.

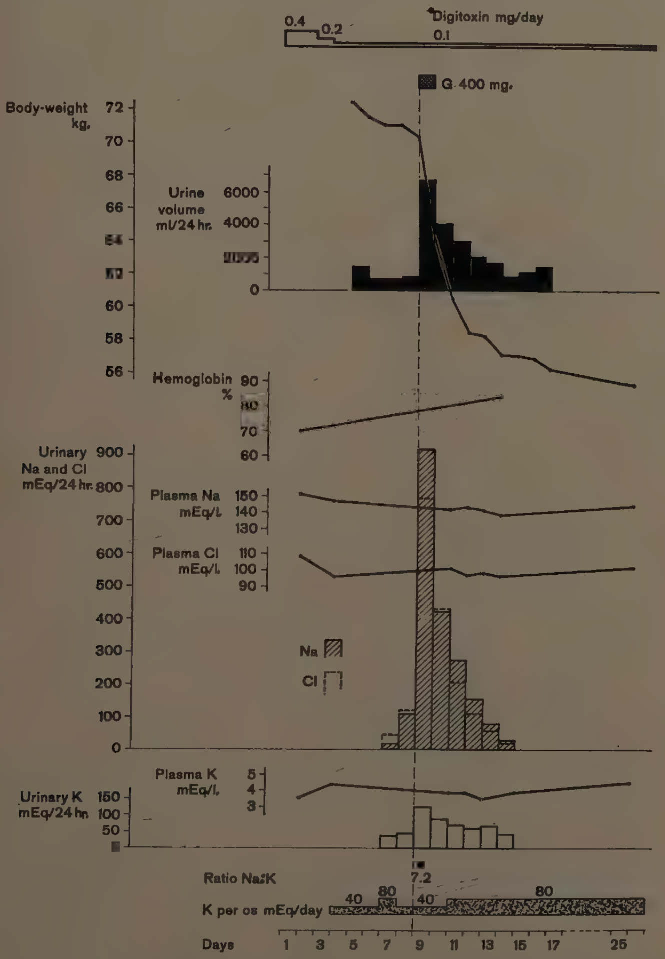

FIGURE 4. Effect of chlorthalidone upon a cardiac patient with edema. The subject, S.O., a 52-year-old female, suffered from hyperthyroidism and congestive cardiac insufficiency. A strict salt-free diet was observed.

We frequently observed that sodium diuresis was extended for several days after administration of a single dose of chlorthalidone.

Several patients received the same dose of 200 mg. chlorthalidone for 3 and 4 days in succession. The drug was well tolerated, and we observed that the diuretic effect persisted as long as water retention continued. However, we

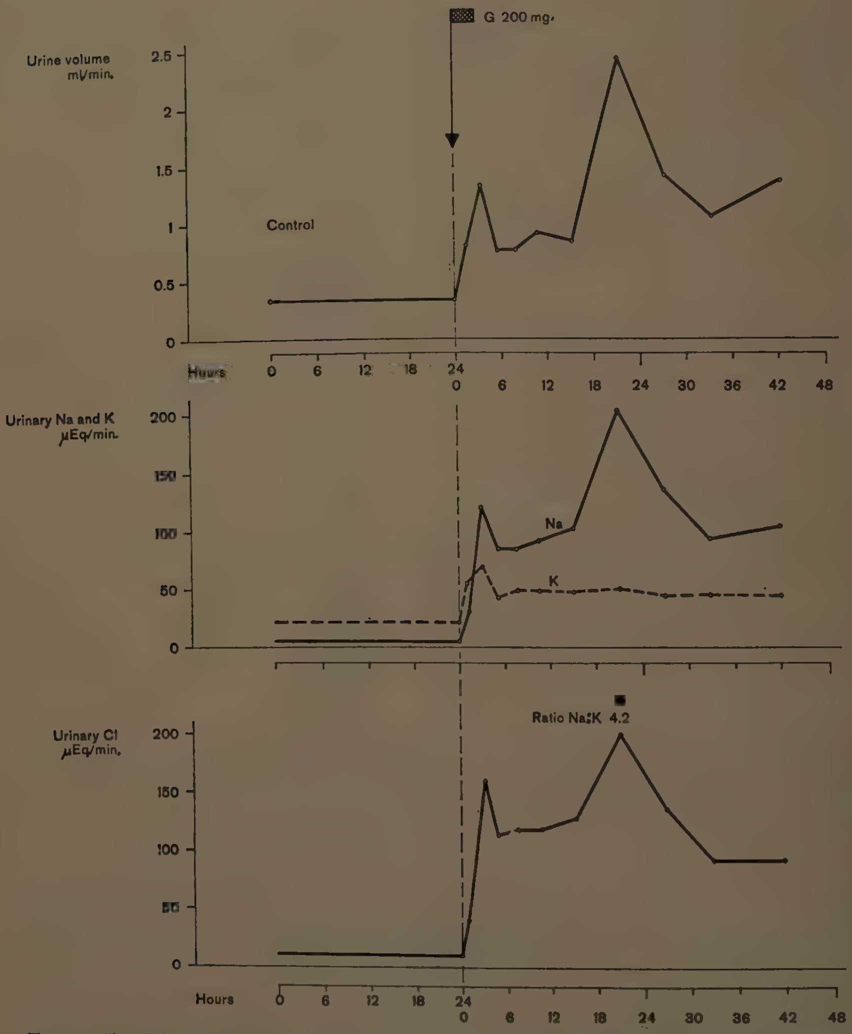

FIGURE 5. Effect of 200 mg. of chlorthalidone studied over 3-hour periods in a cardiac patient with edema. The subject, J.M., a 47-year-old male, suffered from essential arterial hypertension and congestive cardiac insufficiency. A strict salt-free diet was observed.

found it preferable to space the administration of the diuretic to take advantage of the prolonged effect of the medication on subsequent days.

FIGURE 5 shows the effect of administration of 200 mg. chlorthalidone in a decompensated hypertensive patient with congestive cardiac insufficiency. In spite of rest, a strict salt-free diet, and cardiotonic agents, this patient excreted only 6 mEq. of sodium every 24 hours, or 4.2 μEq./min. The natriuretic effect was observed within the first 3 hours following administration of the medication, and was prolonged over 48 hours with a maximum after 18 hours. The potassium effect also exceeded 48 hours. This patient excreted 325 mEq. of sodium and 134 mEq. of potassium in 2 days.

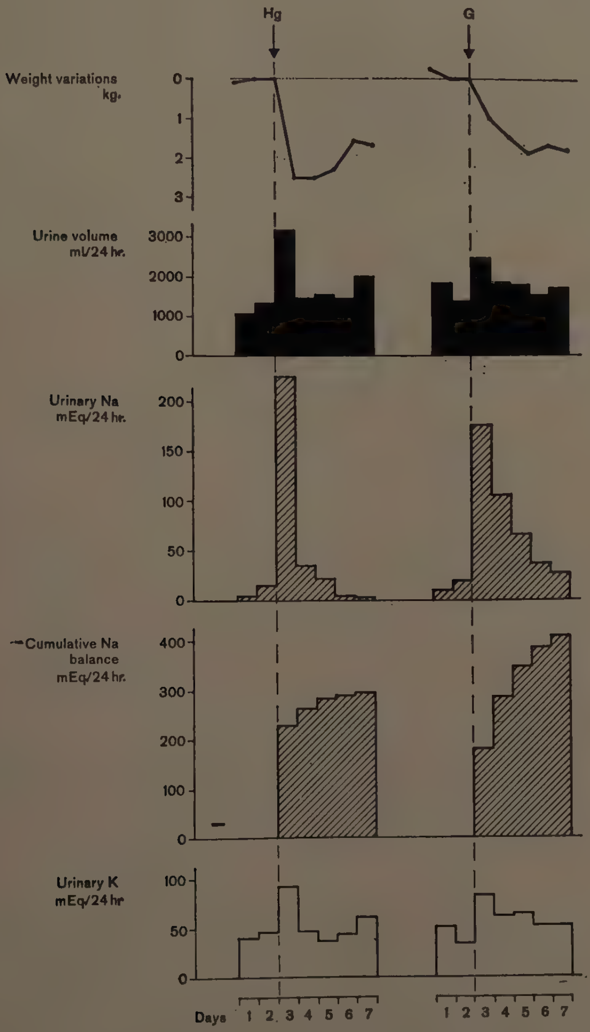

FIGURE 6. Mean data from four cases, comparing the effects of chlorthalidone and a mercurial diuretic. All subjects observed strict salt-free diets.

This prolonged diuretic effect is opposed to that observed for mercurial diuretics. We administered successively to four edematous patients the two kinds of diuretics, at intervals of at least one week: either 200 to 600 mg. of chlorthalidone per os to start and, one week later, 1 or 2 ml. of mercaptomerine subcutaneously, associated with ammonium chloride acidification, or the same drugs in reverse order. Two patients received first the injection of the mercurial diuretic, and two of the patients received first the chlorthalidone. The means of the results, shown in FIGURE 6, indicate that the mercurial diuretic produces a very high sodium diuresis on the day of administration, but that its action is very rapidly exhausted. The weight loss of the first day is not maintained. The chlorthalidone causes a less pronounced sodium excretion, but its effect persists for several days, with the consequence that the total elimination of sodium over a 5-day period is more significant.

The excretion of potassium is less pronounced on the first day with chlorthalidone than with the mercurial diuretic, but it is prolonged for several days.

In another group of experiments we studied the effect of chlorthalidone upon two patients with diabetes insipidus. It is known that a saluretic diuretic, when administered in association with a strict salt-free diet, temporarily reduces the polyuria of such patients.[3] Administration of 200 mg. of the medication resulted in urinary excretion of 233 mEq. of sodium on the first day, and 87 mEq. on the second; diuresis decreased from 5 to less than 3 l., and the patient spontaneously declared that he felt much less thirsty (FIGURE 7). The osmolarity (mOsm./l.) of the urine increased not only on the day of administration of the diuretic, but remained above 150 mOsm./l. for 3 days before decreasing again. This again illustrates the prolonged action of the diuretic.

The administration of 200 mg. chlorthalidone to another patient with diabetes insipidus resulted in an analogous reaction.

Conditions of nonresponse to diuretics. To estimate the value of a diuretic it is necessary to be able to study it under comparable conditions; it is very difficult to define precisely the state of receptivity of the patient to the diuretic in view of the numerous factors involved, such as myocardiac condition, hemodynamics, renal function, and hormonal secretions.

Study of previous quantitative determinations (R. Veyrat and his coworkers[4,5,6]) brought us to the conclusion that it is the degree of urinary sodium elimination that makes possible a better evaluation of the stage of the patient's illness and his ability to respond to diuretics. When the patient, under the most favorable conditions, excretes less than 5 mEq. of sodium per day, it is fairly safe to predict that the diuretic will have little effect. In other words, before the intervention of the medication, the sodium excretion in itself is one of the best prognostic elements concerning water retention and its remedies.

FIGURES 8 and 9 show the means of urinary excretion obtained with the same dose of diuretic administered to patients on a strict salt-free diet, grouped according to the quantity of sodium contained in the urine 24 hours before administration of medication. We found in cardiac as well as in cirrhotic patients that in all cases where sodium excretion exceeded 10 mEq./day, whatever the previous diet, elimination of the edema was easy. When the urinary sodium was between 5 and 10 mEq., the diuretic effect was less spectacular; when the urinary sodium was reduced to 1 or 2 mEq./24 hours, edema was very difficult to eliminate. Even with increased doses of the medication (FIGURE 10) some patients were completely refractory.

It is important to take into account the initial urinary sodium in order to

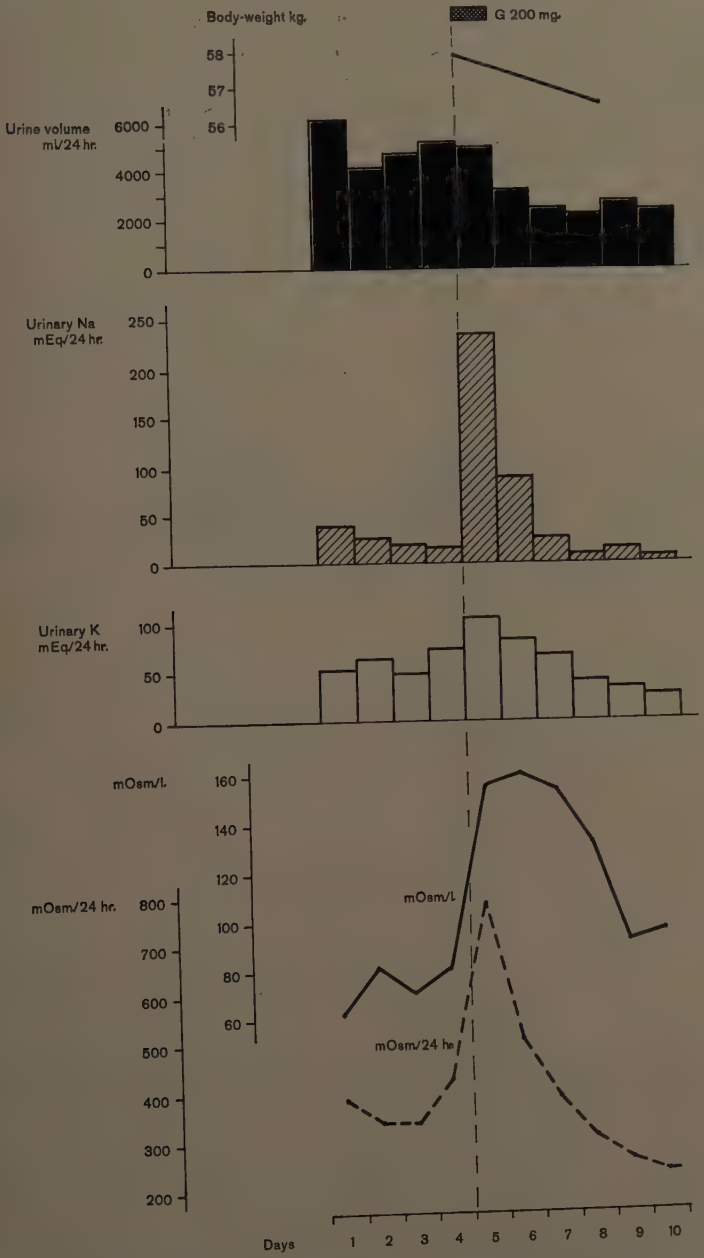

FIGURE 7. Effect of 200 mg. of chlorthalidone upon a patient, M.G., a 49-year-old female with diabetes insipidus following hypophysectomy, who observed a low-salt diet.

evaluate a diuretic medication. The effect of the medication and the prognosis of the disease can be deduced from a difference of a few mEq. of sodium in the 24-hour urine.

Among the patients of the third group, who did not react to the diuretic, we tried to determine whether the very low urinary sodium corresponded to an increase in urinary aldosterone values according to the studies of Luetscher[7] and others.[8,9,10] This was, in effect, what we found, but with urinary aldosterone values varying considerably from one patient to another, it was less the value itself that conditioned urinary retention than the variations within the same patient. FIGURES 11 and 12 show the ineffectiveness of a diuretic administered to patients with much reduced sodium excretion, with 25 μg. and 40 μg. urinary aldosterone every 24 hours and a secretion rate of 1065 μg./24 hr. FIGURE 13 shows an important increase of urinary aldosterone in a patient following paracentesis and the total ineffectiveness of the diuretic at that time.

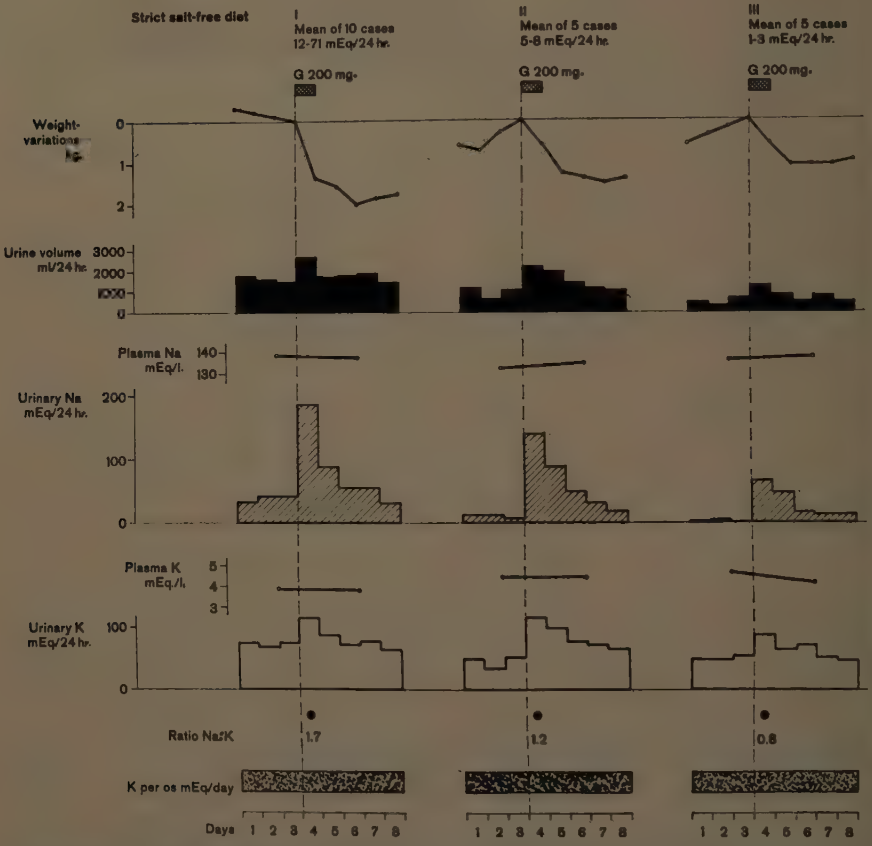

FIGURE 8. Mean diuresis produced in 20 cardiac edema cases with the administration of a single dose of 200 mg. of chlorthalidone to each patient. The cases are grouped according to the initial natriuria values. All the subjects observed strict salt-free diets.

All the factors that disturb the hemodynamics of a cardiac or cirrhotic patient—physical effort,[10] orthostasis,[11] and paracentesis—contribute to the increase in secretion of aldosterone and to the ineffectiveness of the diuretics. All the intervening factors that improve the hemodynamic situation—rest, cardiotonic agents, a strict salt-free diet, diuretics, phlebotomy, correction of disturbances in cardiac rhythm, and improved oxygenation of arterial blood[4]—are capable of lowering the aldosterone and facilitating improved sodium elimination.

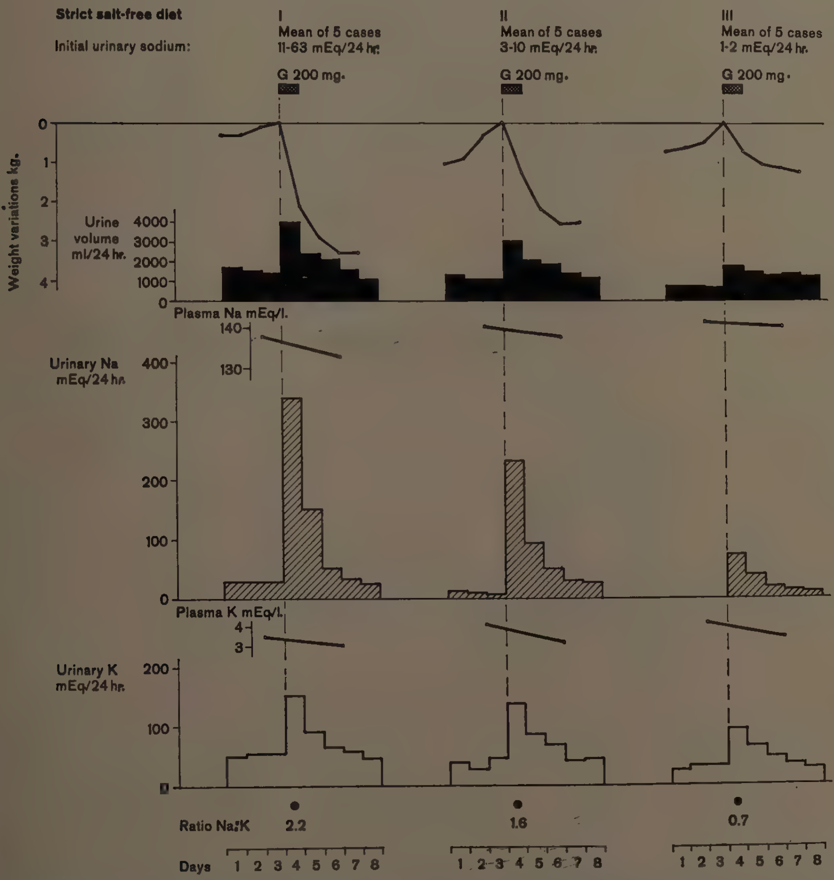

FIGURE 9. Mean diuresis produced in 15 cases of cirrhosis-with-ascites by the administration of 200 mg. of chlorthalidone to each patient. The cases are grouped according to the initial natriuria values. All the subjects observed strict salt-free diets.

FIGURE 14 shows the evolution of aldosteronuria in a patient with chronic pulmonary heart condition and extensive edema, who was from the beginning resistant to therapy. It was not until artifical respiration with the Engström respirator was attempted that the aldosteronuria was lowered and diuresis commenced.

All sodium retention and all failure to respond to diuretics cannot be explained by increased aldosterone secretion alone. As the cardiac muscle becomes completely deficient and the glomerular filtrate is excessively diminished, or when there is a nephropathic component, diuretics are no longer effective.

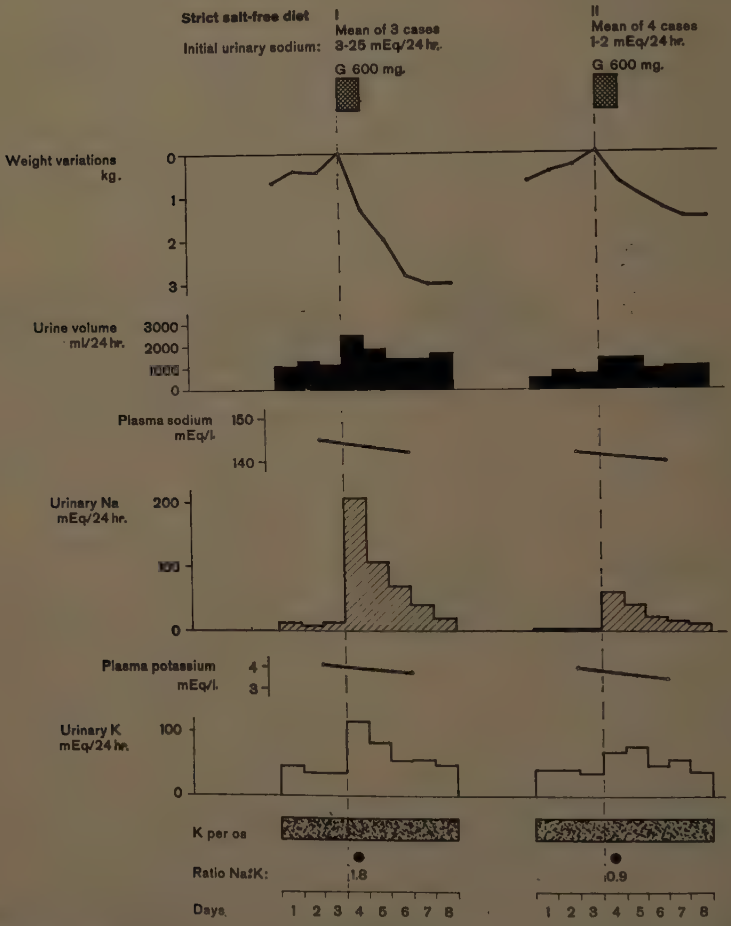

FIGURE 10. Mean diuresis produced with a large single dose of chlorthalidone, administered to 7 patients with edema. The cases are grouped according to the initial natriuria values. All the subjects were on strict salt-free diets.

It is important to understand the role of aldosterone in the salt retention of cardiac and cirrhotic patients before using medications to eliminate this hypersecretion or to inhibit its action, on the one hand, and to avoid, on the other, intervening factors that would increase it.

Resistant edemas and their treatment with prednisone or spirolactones. In certain cases of edema that were resistant to treatment with diuretics, even in

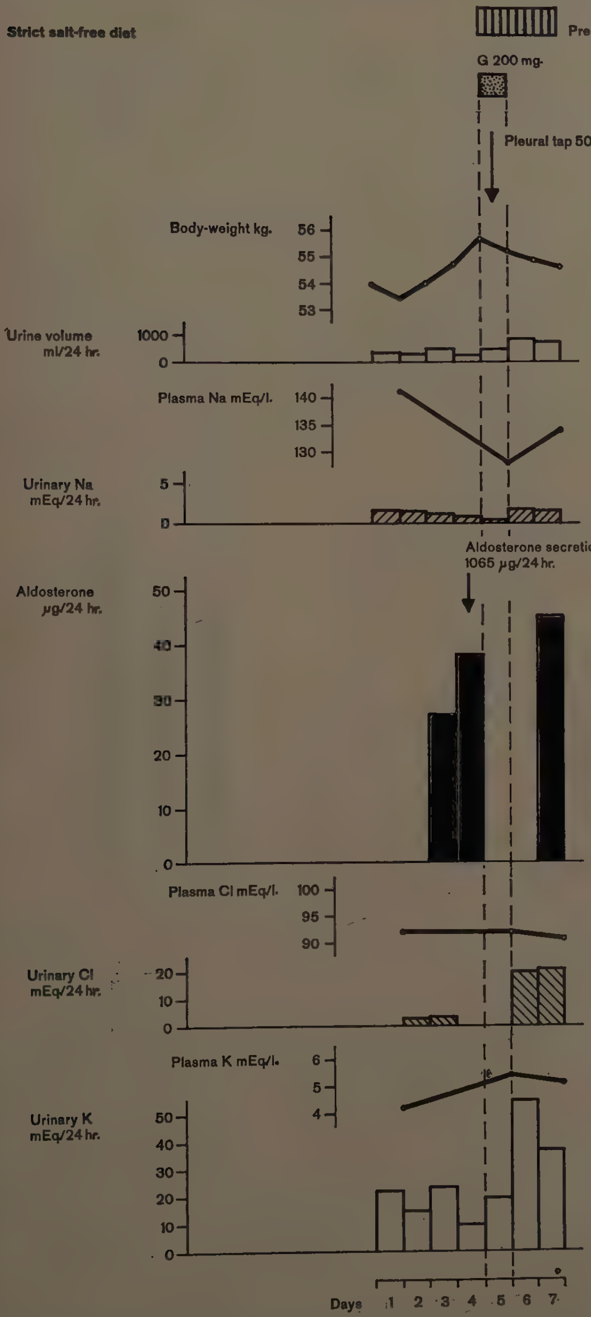

FIGURE 11. Ineffectiveness of the diuretic in a patient, A.L., a 55-year-old female, with low initial natriuria and high aldosterone secretion. Subject, who observed a strict salt-free diet, suffered from refractory congestive cardiac insufficiency.

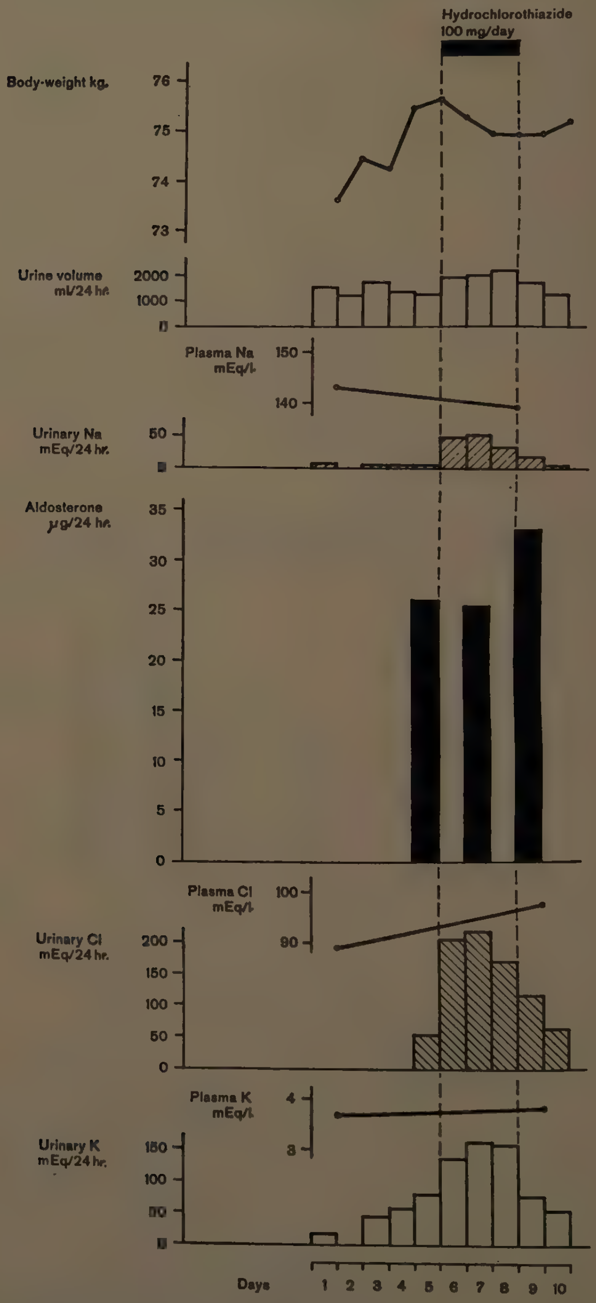

FIGURE 12. Ineffectiveness of the diuretic in a patient, E.N., a 66-year-old male, with low initial natriuria and high aldosteronuria. Note the high potassium excretion and slight sodium excretion. Patient, who observed a strict salt-free diet, suffered from chronic cor pulmonale.

large doses, we attempted to combine administration of diuretics with a form of therapy capable of making them effective.

In numerous cases, natriuresis was increased by prednisone alone. In other cases, this drug reestablished effectiveness of a diuretic that had become inactive when administered alone (FIGURE 15). We have observed repeatedly that urinary aldosterone values decrease when prednisone is administered.

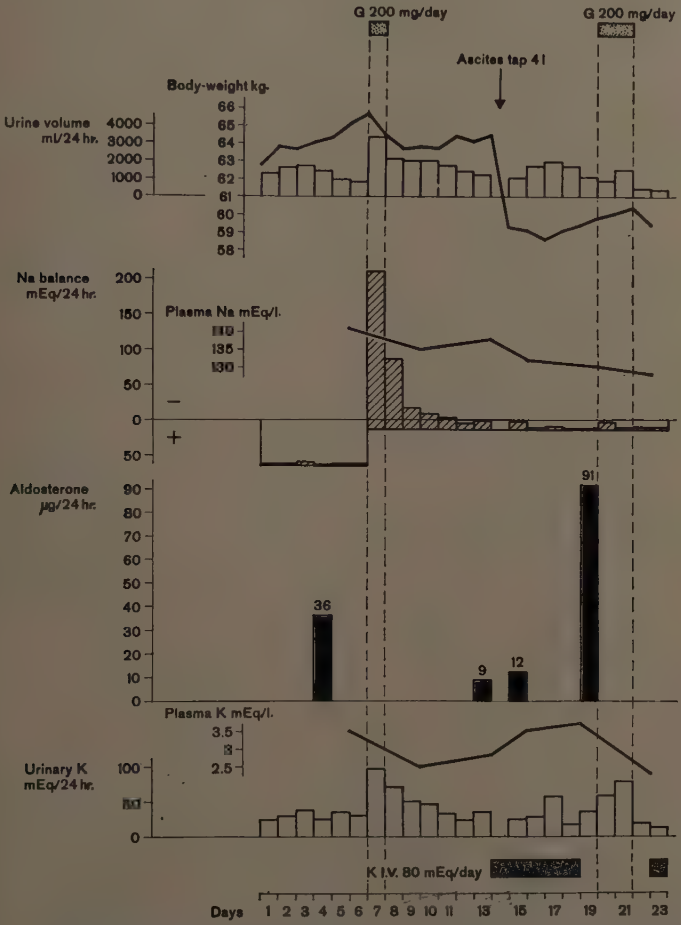

FIGURE 13. Ineffectiveness of a single dose of the diuretic in a patient, H.J., a 56-year-old male, following tapping of ascites, which increases aldosteronuria. The subject, who observed a strict salt-free diet, suffered from Laennec's cirrhosis.

A particular place should be given to compounds that are capable of inhibiting aldosterone secretion or action. In this respect, spirolactone can be considered the most effective.[13] As shown in FIGURE 16, a cirrhotic patient with ascites, who did not respond to chlorthalidone, mercaptomerine, and spirolactone when given alone, responded with a massive sodium diuresis to a combination of spirolactone and chlorthalidone, despite severe hyperaldosteronuria. Secretion of aldosterone was not decreased. Its action at the tubular level was, however, reduced. Due to the mechanism of homeostatic regulation, variations in urinary aldosterone excretion are difficult to interpret in this patient.

Untoward side effects of the new diuretics. With more than 500 doses of

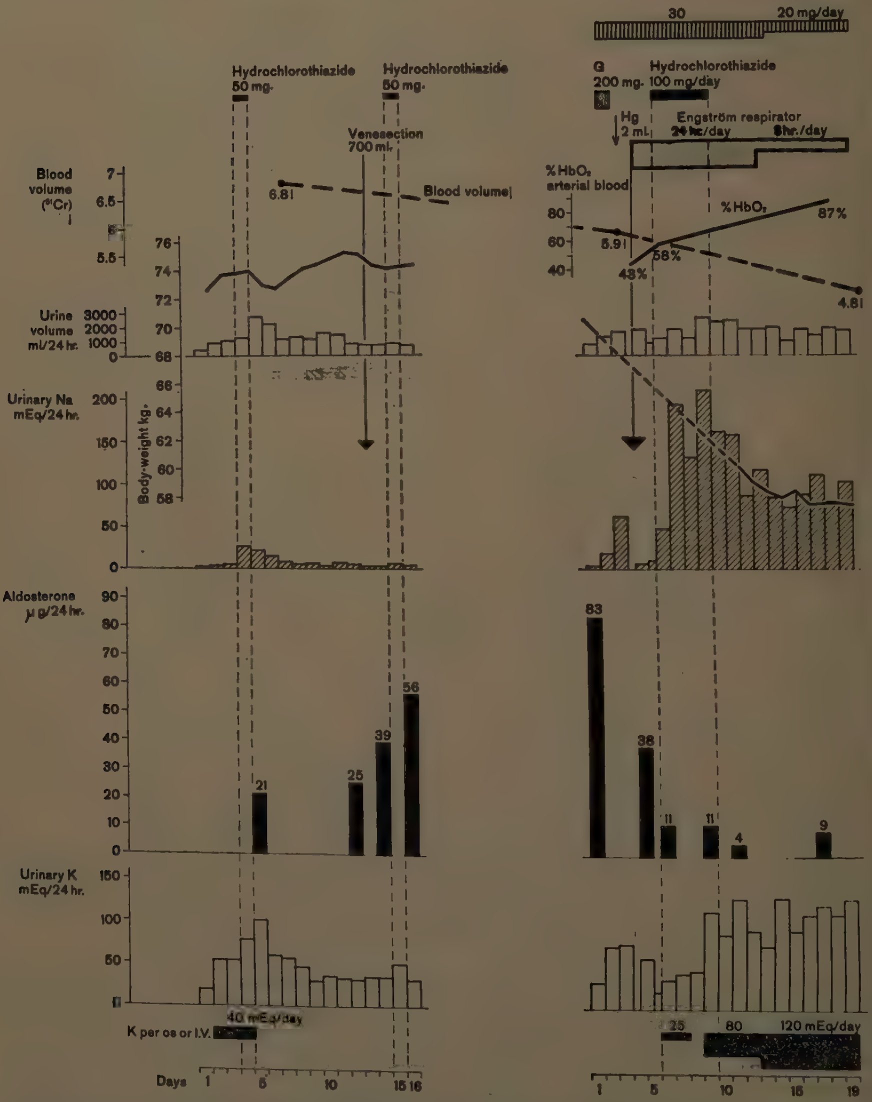

Figure 14. Recurrence of the effectiveness of a diuretic in a patient, R.G., a 50-year-old male, following lowering of aldosteronuria as a result of artificial respiration with an Engström respirator. Patient, who observed a strict salt-free diet, suffered from chronic cor pulmonale.

chlorthalidone given to more than 120 patients, we did not observe any signs of drug intolerance that could be attributed to the diuretic, such as cutaneous allergic reactions, changes in the blood counts, or urinary sediment or changes in hepatic or renal function. We found an increase in neither the blood creatinine level nor the blood urea nitrogen level following administration of the drug. In one patient, a brief episode of diarrhea coincided on two occassions with administration of chlorthalidone.

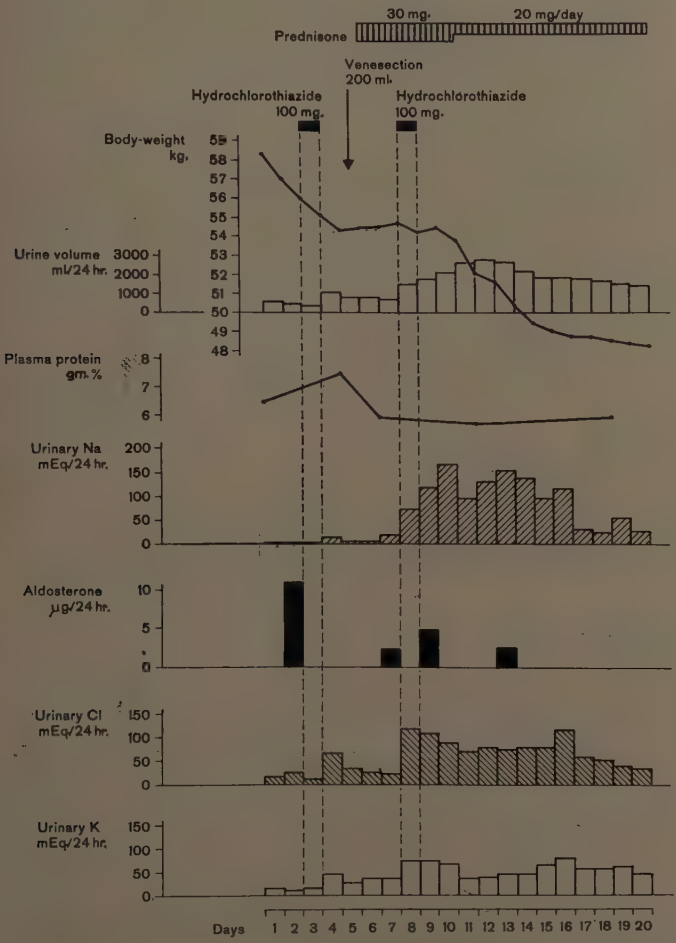

FIGURE 15. Recurrence of the effectiveness of a diuretic, hydrochlorothiazide, used in conjunction with prednisone treatment, in lowering of aldosteronuria. The patient, F.W., a 56-year-old male, suffered from chronic cor pulmonale and observed a strict salt-free diet.

We must stress, on the other hand, the potassium loss caused by the use of diuretics, which can have undesirable consequences that are related to the appearance of hypokalemia.

The urinary excretion of potassium is of the order of 150 to 250 mEq. for three days following a single dose of the diuretic. It is therefore necessary to be cautious when repeating this therapy several times with patients who do not eat well and, therefore, cannot compensate this loss.

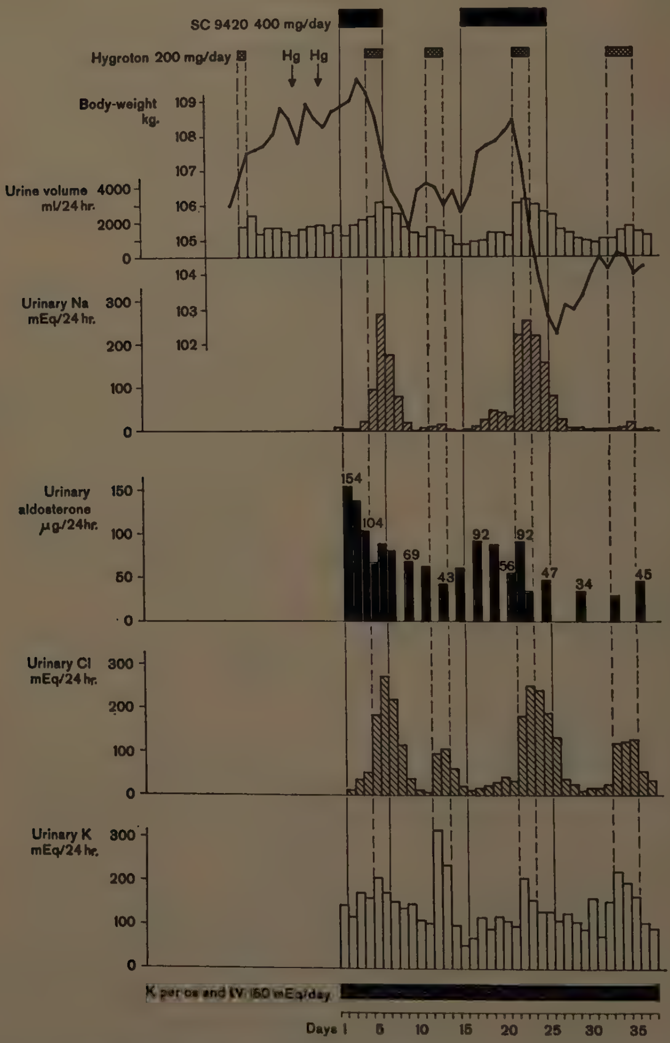

FIGURE 16. Effect of 400 mg. spirolactone, SC 9420, in A.B., a 52-year-old male patient with Laennec's cirrhosis. The spontaneous excretion of sodium increases, and the diuretic regains its effectiveness.

It is also important to remember, as studies with K_{42} have shown (C. Nagant de Deuxchaisnes *et al.*[12]), that cardiac and cirrhotic patients, particularly women, have a very reduced reserve of potassium, at times as little as 1300 mEq. One can imagine the effect of potassium loss when such patients receive a diuretic twice a week without potassium supplements.

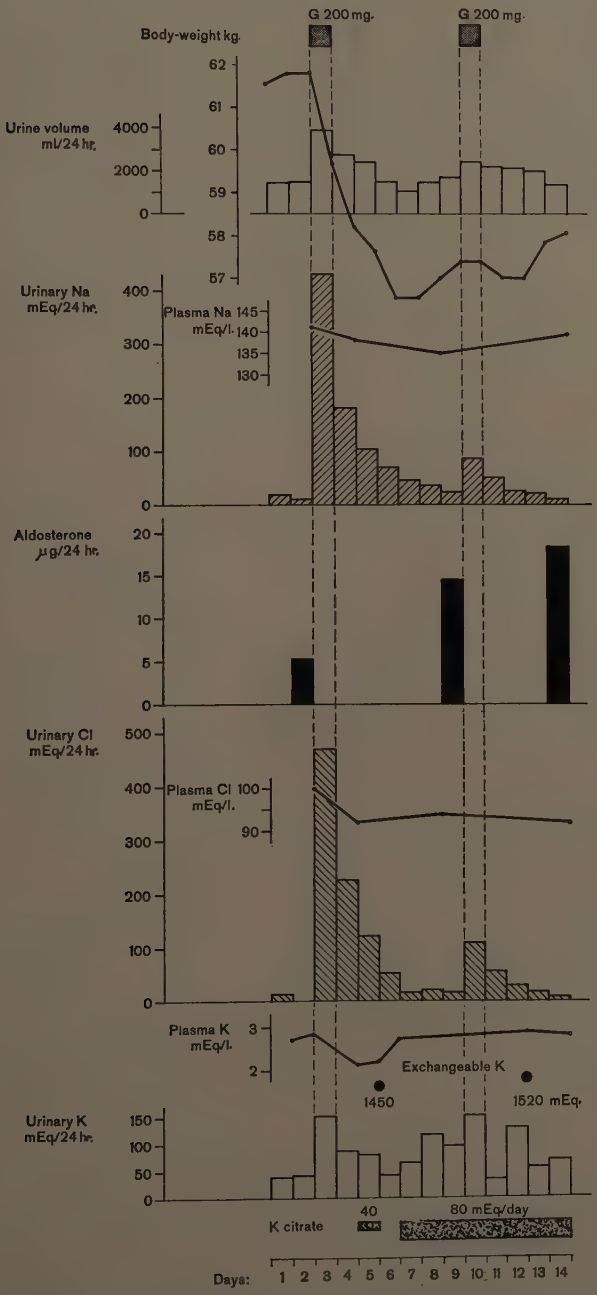

FIGURE 17. Accentuation of hypokalemia when the diuretic is administered without a surplus of potassium to a cirrhotic, G.C., a 56-year-old female. The patient, suffering from Laennec's cirrhosis, had a total body potassium reduced to 1450 mEq.

FIGURE 17 shows an example of hypokalemia in a woman with cirrhosis and ascites, whose potassium reserve was reduced to 1450 mEq. Prophylactic treatment with excess potassium prevented a new fall in kalemia.

The potassium loss, although very poorly tolerated by cardiac patients with rhythmical difficulties or those sensitive to digitalis, is not a contraindication to the administration of diuretics, since it can be remedied by the introduction of potassium into the diet and by administration of sufficient doses of potassium chloride. But it must be considered in these cases.

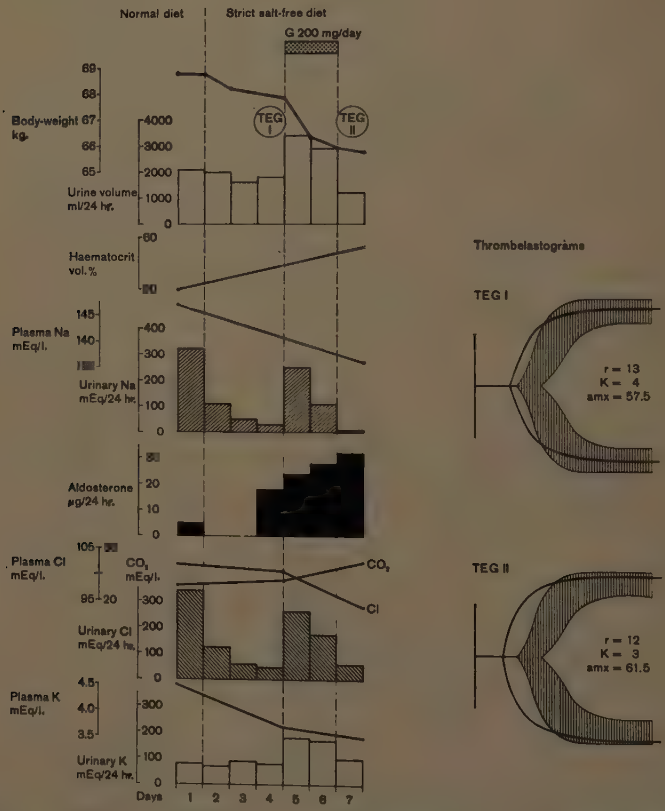

FIGURE 18. Effect of the diuretic in a normal subject, M.G., a 28-year-old male who observed a salt-free diet. The subject experienced dehydration from lack of salt and a change in his thrombelastogram.

In cases where prolonged administration of diuretics is employed when there is no water retention (mainly in hypertensives), or where the diuresis produced is too abrupt, the patients are exposed to a danger whose primary manifestation is a tendency to thrombophilia; we were able to confirm this with the thrombelastograms. It is, therefore, wise to administer an anticoagulant in cases where very intense diuresis is anticipated.

FIGURES 18 and 19 show the effect of high doses of diuretics upon normal subjects maintained on a strict salt-free diet. We see here a dehydration resulting from lack of salt with hyponatremia, hypokalemia, hypochloremic alkalosis, hyperproteinemia, and an increase in the hematocrit reading, which is accompanied by changes in the thrombelastogram. The curve is located entirely within the zone of hypercoagulability because of the shortened reaction and coagulation times and the amplitude of the curve.

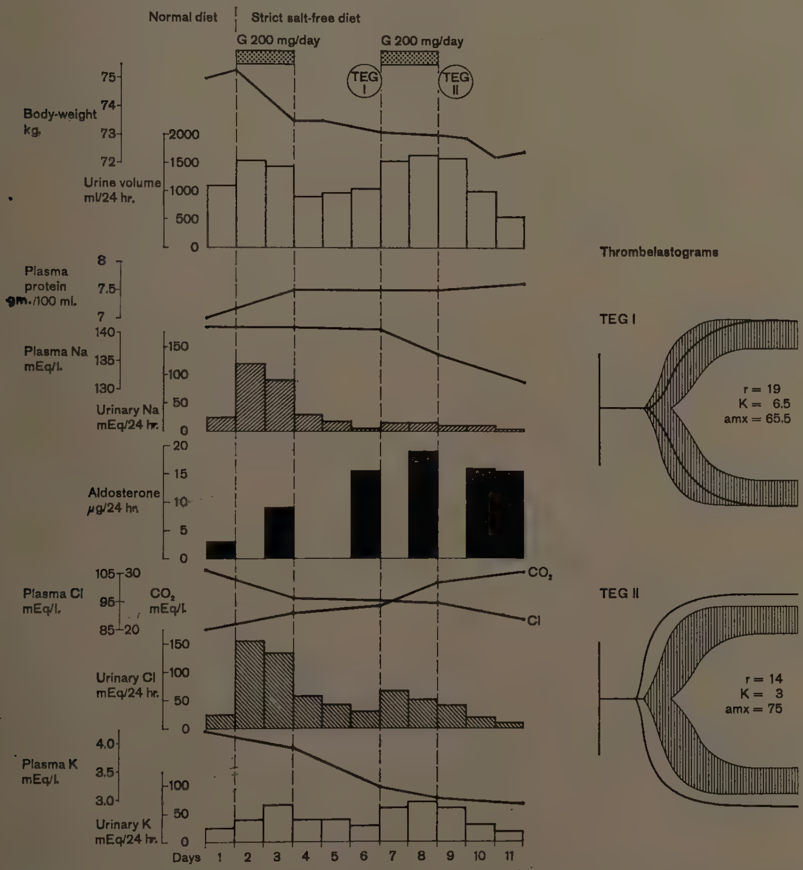

FIGURE 19. Change in the thrombelastogram produced by a loss of salt in a normal patient, B.M., a 55-year-old female.

Conclusions and Summary

(1) A single dose of chlorthalidone, administered orally, caused an elimination of sodium and chloride in approximately equal quantities, in five normal subjects. Two hours after administration, the sodium diuretic effect appeared and, although it was most pronounced during the first 12 hours, continued for more than 24 hours. The duration of action of chlorthalidone is clearly longer than that of chlorothiazide. The logarithm of the dose plotted against the sodium excretion gave a straight line. With high doses of chlorthalidone po-

tassium excretion was also increased, but the Na:K ratio remained high. The urinary excretion of bicarbonates increased slightly, and the *p*H of the urine, although increased, did not reach neutrality, thus suggesting an inhibition of carbonic anhydrase.

(2) In 120 edematous patients with congestive heart failure or hepatic cirrhosis with ascites, a single dose of chlorthalidone (100 to 600 mg., but usually 200 mg.) had, in general, a marked sodium diuretic effect. The cumulative balance studies showed that a single dose of chlorthalidone can produce a greater sodium diuresis than an injection of a mercurial diuretic. In addition the sodium excretion continued for several days and the edema was eliminated gradually.

(3) It was shown that the response of an edematous patient to diuretics can be predicted from the urinary sodium level. If the initial sodium excretion is high, the response is satisfactory; if it is low, the response is very much smaller.

It is very important to pay special attention to the initial spontaneous sodium excretion in order to evaluate the efficiency of a diuretic and to compare similar cases.

(4) The excretion of aldosterone was determined in patients who did not respond to diuretics and in whom the initial urinary sodium was very low. In the absence of renal disorder, the failure of patients to respond to diuretics corresponds to an elevated urinary aldosterone. In such patients improvement of hemodynamic conditions or correction of severe anoxemia may decrease the secondary hyperaldosteronism and thus lead to a better response to diuretic agents.

(5) In cases of refractory edema, improved response to diuretics has been observed following treatment with prednisone or spirolactone.

(6) The undesirable side effects of these diuretics were also studied, particularly the thrombophilic tendency with a decreased reaction time of the thrombelastogram.

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STUDIES ON THE METABOLIC EFFECTS OF SPIRONOLACTONE IN MAN*

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INTRODUCTION

The treatment of certain patients with edema or ascites has been unsatisfactory in the past because of the frequent failure to induce a diuresis and the depletion of potassium when satisfactory diuresis has been obtained. Attempts to solve this problem have resulted in the development of new diuretic compounds for both therapeutic trial and investigations of the mechanisms of edema formation.

It has been shown that the ability of normal persons to conserve sodium in the presence of sodium deprivation is at least in part dependent on the secretion of aldosterone by the adrenal glands.[1-3] Although aldosterone is important in renal sodium retention and increased potassium excretion in man,[4-7] its exact role in the pathogenesis of edematous states is not clear. Conn and Louis[8] first reported the clinical entity of primary aldosteronism, and secondary hyperaldosteronism has been reported in patients with cirrhosis, nephrosis, congestive heart failure, and idiopathic edema.[1,9-14] The importance of a substance that would inhibit either the secretion or the action of aldosterone was apparent. Recently steroid chemists have developed a new series of compounds, the 17-spirolactones, which inhibit the action of aldosterone presumably by competitive inhibition at the renal tubular level.[15-17] This is in contrast to those substances that can produce natriuresis by inhibition of adrenal steroid synthesis.[18,19] The spirolactone SC 9420 (spironolactone) is the first such compound to be effective when taken orally.

The studies by Liddle demonstrated the antialdosterone activity of spironolactone in edematous human beings.[17] These findings have been confirmed and extended in patients with cirrhosis[20,21] and congestive heart failure.[22] Clinical studies have further demonstrated the effects of spironolactone in combination with other diuretics. When spironolactone is used in combination with other diuretics, its natriuretic effect may be more than additive and it decreases the potassium excretion often seen when organomercurials, chlorothiazide, or benzothiadiazine diuretics are used alone.[17,20,21]

The present report will describe studies designed to assess the metabolic effects of spironolactone given orally for 3 to 12 days to 12 patients with fluid retention. Most of these patients either responded poorly or did not respond to other diuretic agents and were selected on this basis.

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MATERIALS AND METHODS

Twelve patients were studied on the medical wards of either the University Hospital or the Birmingham Veterans Administration Hospital. All patients had ascites or edema, or both, and were placed on controlled sodium diets; the following parameters were studied: body weight, serum sodium and potassium concentration, and urinary sodium, potassium, 17-hydroxycorticosteroid, 17-ketosteroid, aldosterone, and creatinine levels.

Three patients had ascites secondary to hepatic cirrhosis, four had edema secondary to congestive heart failure, and three had idiopathic edema without hepatic, cardiac, or renal disease. One patient had edema due to metastatic carcinoma of the prostate and one had diabetes, with anasarca secondary to Kimmelstiel-Wilson's disease. All patients received spironolactone orally for 3 to 12 days in doses of 100 mg. every 6 hours. Urine samples were collected without preservative from 7:00 A.M. to 7:00 A.M. and kept refrigerated.

Urinary aldosterone levels were determined by a modification of the chemical procedure of Nowaczynski *et al.*[23] Normal values for this laboratory range from 2.3 μg. to 13.6 μg./24 hours, with a mean of 6.4 μg. for normal subjects on unrestricted diets.

Creatinine levels were measured by the method of Clark and Thompson.[24] The urinary 17-ketosteroids were extracted by the method of Drekter *et al.*[25] and colorimetry was performed as in the procedure of Holtoroff and Koch.[26] With the use of this method in our laboratory, normal values for males range between 8 and 24 with a mean of 15 mg./24 hours. The 17-hydroxycorticosteriods were determined by a modification[27] of the method of Reddy.[28] Normal values for males in our laboratory range from 1 to 11 with a mean of 5 mg./24 hours.

In order to eliminate the effects of minor inaccuracies in the timing of urine collections, each patient's urine values were corrected according to the average creatinine content of all of his specimens. In all cases, the corrections were small, and where the creatinine levels were so low as to indicate obviously faulty collections, the values were discarded. Blood ammonia levels were determined by Conway's microdiffusion technique.[29]

OBSERVATIONS

Hepatic Cirrhosis

Patient 1 (*W.R.J.*). A 53-year-old white male was admitted to the hospital for therapy of ascites and edema. His history was compatible with biliary cirrhosis in that six years prior to admission he had had nausea, vomiting, right upper quadrant pain, and jaundice. A nonfunctioning gallbladder had been demonstrated radiographically, as well as a gastric ulcer, which had healed with therapy. The jaundice had regressed in two weeks and he had been asymptomatic until one year prior to admission, when he had noted mild swelling of the ankles and abdomen. Five months prior to admission he had noted progressive swelling of the ankles and abdomen and had developed shortness of breath. Medical studies at that time revealed a palpable liver, a Bromsulphalein retention of 20 per cent in 45 min., a serum thymol turbidity of 19 U., and a prothrombin time of 19 sec. He responded well at first to a high-caloric diet, low in sodium, and the administration of mercurial and chlorothiazide diuretics. However, therapy became ineffective in that an adequate diuresis was always accompanied by a cloudy sensorium and asterixis, which would disappear when diuretics were discontinued.

He was a dark-complexioned man with a distended abdomen, who appeared chronically ill. His blood pressure was 120/70 mm. Hg, pulse rate 90/min., respirations 14/min., and temperature 99° F. Numerous spider angiomata were noted over the entire upper body. There was a fruity odor to the breath. No abnormality of the heart and lungs was noted. The abdomen was markedly distended and the liver was palpable 6 cm. below the right costal margin as a firm smooth mass. The spleen was palpated 1 fingerbreadth below the left costal margin. A fluid wave and shifting dullness were easily elicited. The testes were atrophic and there was a noticeable loss of pubic hair. There was a 2+ pretibial and a 3+ ankle edema. The patient's sensorium was cloudy, but there was no flapping tremor.

The complete blood count and urinalysis gave normal values. The Bromsulphalein retention was 44 per cent in 45 min. Serum transaminase was 149 Frankey units. The prothrombin time was 15 sec. The serum total protein was 10.7 gm. and globulin 7.3 gm./100 ml. The serum alkaline phosphatase level was 2 Bessey-Lowry units, and the serologic test for syphilis gave negative results. The serum direct reacting bilirubin level was 1.2 and the indirect 2.15 mg./100 ml.

The patient was placed on a diet low in protein and containing 30 mEq. of sodium, which was continued throughout his hospital course. Attempts to diurese the patient with chlorothiazide and mercurial diuretics were unsuccessful. A paracentesis was performed for relief of respiratory distress and produced a typical ascitic fluid without neoplastic cells.

The response to spironolactone (FIGURE 1) was as follows. The urinary sodium levels on the two days prior to therapy were 4 and 2 mEq./24 hours, and the potassium levels were 25 and 19 mEq./24 hours. During the administration of spironolactone his sodium excretion rose to a maximum of 95 mEq./24 hours on the fourth day of therapy and the potassium excretion fell to 8 mEq./total volume. The patient's weight decreased from 133 to 128 lb. during the four days of therapy. His urinary aldosterone levels were relatively constant throughout this period. He received no therapy for two weeks after the above four-day period of therapy, and control urine values prior to the second administration of spironolactone revealed a sodium level of 8 and potassium level of 48 mEq./24 hours. On the second course of spironolactone therapy the sodium levels increased to an average of 125 mEq./24 hours, two peaks being reached, one on the second day and the other on the last day of this seven-day period of therapy. Forty-eight hours after the drug was discontinued the sodium excretion had again fallen to 15 mEq. while potassium had risen to 50 mEq./total volume; however, the patient continued to lose weight during this time. Again there were no significant changes in the urinary aldosterone levels. There were no changes in the urinary 17-hydroxycorticosteroid levels, but on both occasions there was a slight rise noted in the urinary 17-ketosteroid levels.

Because of this patient's excellent clinical response, he was given six subsequent 10-day periods of spironolactone therapy, each time receiving 400 mg. daily orally in divided doses. On each occasion his weight decreased 8 to 10 lb. and his abdominal girth decreased from 1 to 2 inches; subjectively he felt much improved. There has been no sign of hematological, renal, cutaneous, or neurological toxicity.

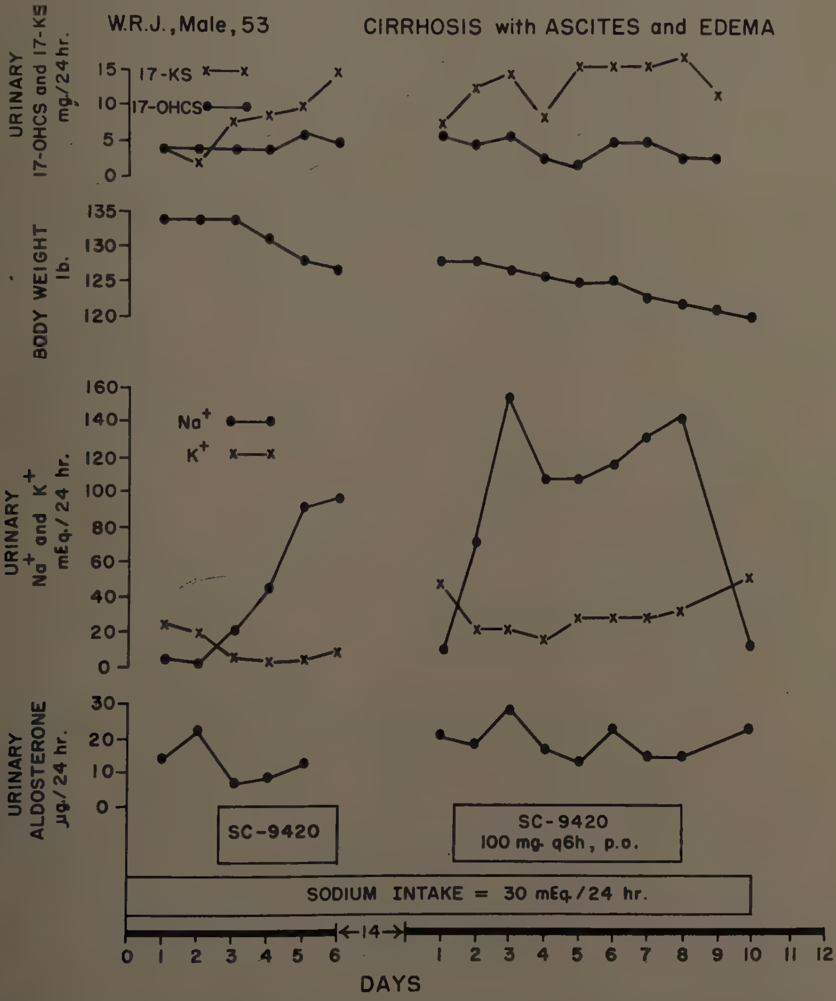

FIGURE 1. The effects of spironolactone administration on body weight and urinary sodium, potassium, aldosterone, 17-hydroxycorticosteroid, and 17-ketosteroid levels in patient 1 with hepatic cirrhosis, ascites and edema.

Patient 2 (T.S.M.). A 53-year-old white male had the classic history and physical findings of cirrhosis of the liver. In August 1957 he had a portacaval shunt because of bleeding esophageal varices. He did well for 3 months postoperatively, after which he again developed ascites and pedal edema that continued despite diuretic therapy. The patient had no evidence of cardiac or renal disease. He was admitted to the hospital after an episode of bleeding from esophageal varices. His blood ammonia level was 1200 μg./100 ml., and he showed signs of impending hepatic coma. He responded well to oral neomycin and magnesium sulfate catharsis. His blood ammonia decreased to 900 μg. during the first 24 hours and to 184 μg. during the subsequent 24 hours of therapy. The patient failed to diurese with mercurial and chlorothiazide diuretics and was given spironolactone for 10 days.

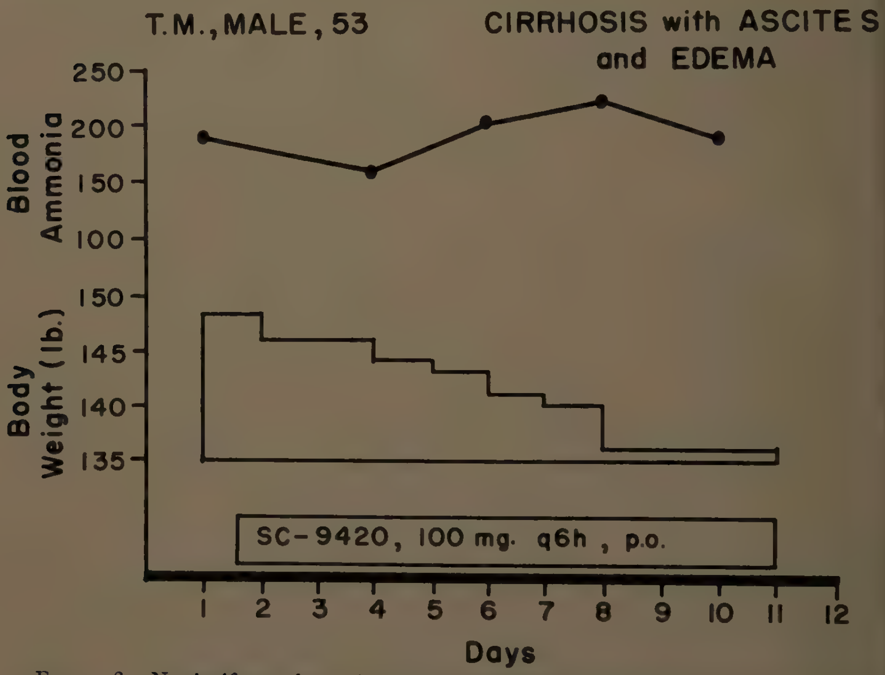

FIGURE 2. No significant change in the blood ammonia levels occurred in patient 2 with hepatic cirrhosis, who lost 12 lb. during spironolactone therapy.

The response to spironolactone (FIGURE 2) was as follows. The patient's body weight fell from 148 to 139½ lb. during this 10-day period; his blood ammonia levels did not change significantly. His urinary aldosterone levels were unchanged, and there were no changes in the urinary 17-hydroxycorticosteroids. The urinary 17-ketosteroids increased slightly. There was no evidence of hematological, renal, cutaneous, or neurological toxicity.

The patient was readmitted to the hospital approximately five months later because of anemia, mental confusion, and recurrent pedal edema and ascites. His weight was 146 lb. The patient was given spironolactone for five days, and his weight decreased to 138 lb. His blood ammonia levels again did not change appreciably, and the only change in serum electrolytes on either occasion was a slight increase in the serum potassium during both periods of spironolactone therapy.

Patient 3 (*N.Y.*). A 43-year-old white female with hepatic cirrhosis, ascites, and generalized edema was admitted to the hospital, critically ill as the result of bleeding esophageal varices. The hemorrhage was controlled, but the ascites and generalized edema persisted despite diuretic agents. The patient was placed on spironolactone for seven days.

The response to spironolactone was as follows. During the period of therapy the patient had two severe episodes of gastrointestinal bleeding with peripheral vascular collapse. This was treated with blood transfusions and vasopressors prior to her death. There was no response to spironolactone therapy in this critically ill patient, who died 15 days later.

Comment. In two of three patients with hepatic cirrhosis, spironolactone administration resulted in weight loss and sodium and water diuresis. The patient who did not respond was critically ill with circulatory collapse. One patient received a total of 25 gm. of spironolactone in repeated courses and lost 8 to 10 lb. and 1 to 2 inches in girth during each period of therapy. There were no signs of toxicity in these three patients. Blood ammonia levels did not change during spironolactone therapy in either of the two patients with cirrhosis in whom these were followed.

Arteriosclerotic Heart Disease

Patient 4 (*W.R.*). An 84-year-old white male with arteriosclerotic heart disease and generalized arteriosclerosis was admitted to the hospital because of congestive heart failure. On previous hospital admissions he had responded well to diuretics and digitalis except for mild residual pedal edema. On this admission digitalis was increased until signs of toxicity appeared and diuretics again were given. Although some weight loss was initially obtained with mercurial and chlorothiazide diuretics, a moderate pedal edema remained. The patient's body weight had stabilized at 149 lb.

The response to spironolactone (FIGURE 3) was as follows. The patient was given spironolactone orally for five days; his body weight decreased to 140 lb. and his pedal edema completely disappeared. Urinary adlosterone levels, which before therapy had averaged 14 μg./day, did not change significantly. No change was noted in the urinary 17-hydroxycorticosteroids, although again the urinary 17-ketosteroids increased slightly. His dyspnea on exertion lessened markedly, and his blood urea nitrogen, which had been 34 mg./100 ml. before spironolactone therapy, dropped to 28 with the diuresis. Two weeks after the drug was discontinued his weight had again risen to 146 lb. and there was a 1+ pedal edema.

Patient 5 (*E.C.V.*). A 69-year-old white male with hypertensive cardiovascular disease and arteriosclerotic heart disease was admitted with congestive heart failure several hours after an episode of chest pain characteristic of myocardial infarction. He was treated for congestive heart failure and myocardial infarction and improved somewhat over the next few days, although some orthopnea and pedal edema continued. No diuresis was obtained with meralluride, and acetazoleamide therapy resulted in a slight but temporary diuresis. A repeat chest film showed clearing of loculating fluid in the right hemithorax, thus revealing a mass that was thought to represent a bronchogenic carcinoma.

As the patient was no longer responding to therapy, all diuretics were discontinued for five days prior to spironolactone therapy.

The response to spironolactone combined with other diruetics (FIGURE 4) was as follows. During the period without therapy the patient gained weight: from 174 to 180 lb. During the first three days of acetazoleamide therapy he lost 2 lb. Acetazoleamide was continued, and on the fourth day 1 cc. of meralluride was administered intramuscularly and the patient lost 2 lb. more. On the sixth day spironolactone was added to the program of treatment. During the next four days he lost 4 lb. On the fifth day of spironolactone therapy, 1 cc. of meralluride was again given intramuscularly, in order to combine the effects of all three diuretics. The patient lost 7 lb. during the next 24 hours, as compared to the 2 lb. lost with each of the other two diuretics without

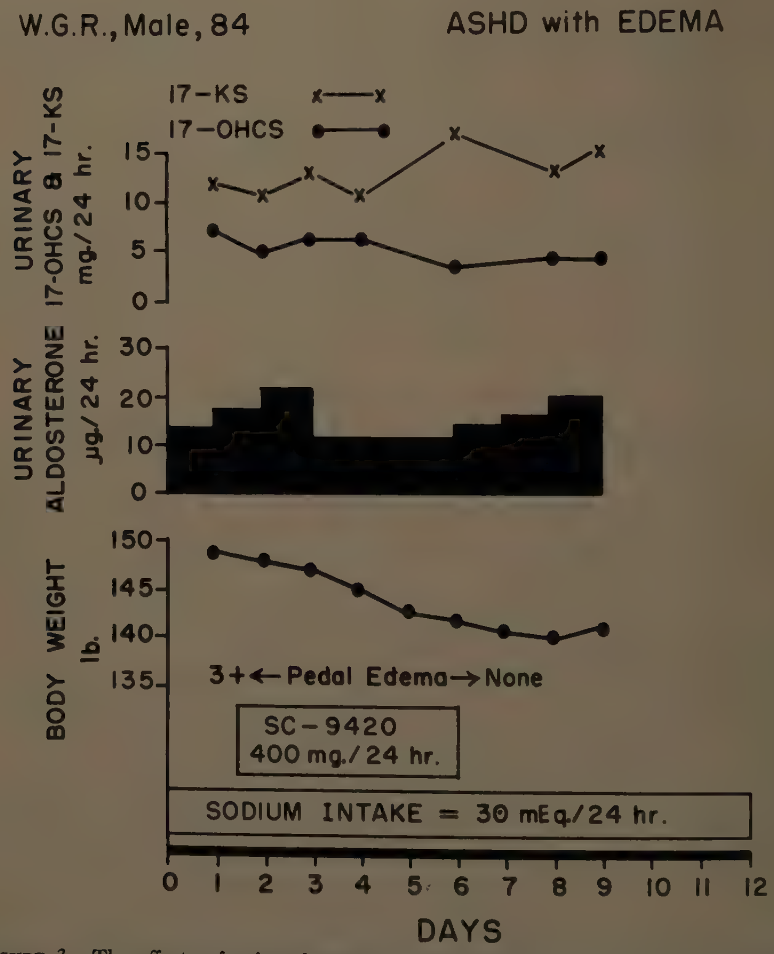

FIGURE 3. The effects of spironolactone on body weight, edema, and urinary steroid excretion in patient 4 with arteriosclerotic heart disease and edema.

spironolactone. On the fifth day he also developed a severe pruritic maculopapular rash over his entire body. Spironolactone was discontinued, and the administration of an antihistamine immediately relieved the pruritus. The patient felt much better the following day, although somewhat sleepy because of lack of rest the night before, due to nocturia. The rash had almost disappeared during these 24 hours. Two days later he complained of sudden severe chest pain and shortness of breath, and died shortly thereafter.

Post-mortem examination confirmed the presence of bronchogenic carcinoma with metastases and the presence of generalized arteriosclerotic changes.

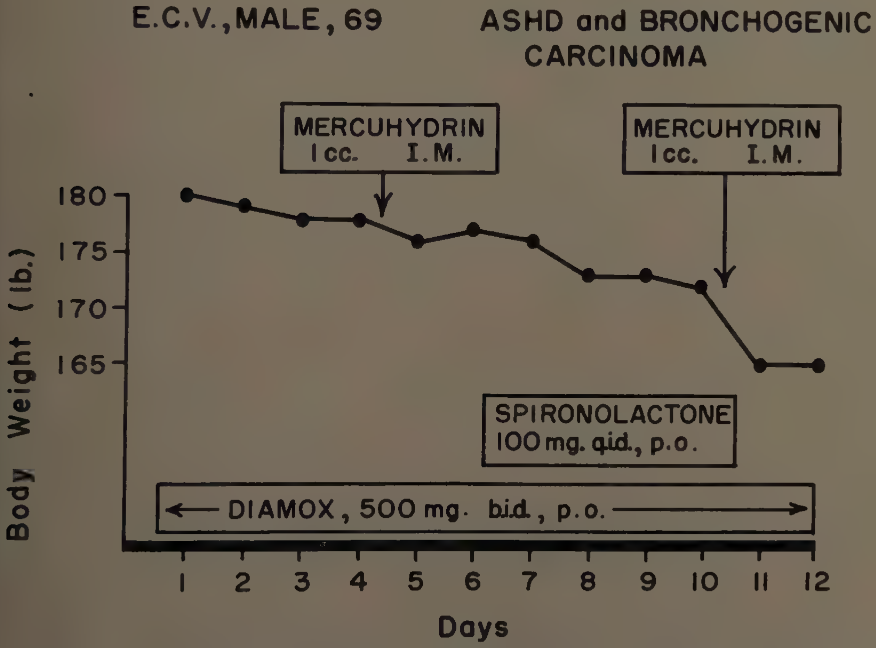

FIGURE 4. Spironolactone combined with acetazoleamide (Diamox) and meralluride (Mercuhydrin) in patient 5 with arteriosclerotic heart disease, bronchogenic carcinoma, and edema.

There was no evidence of hematological, hepatic, renal, or neurological toxicity to spironolactone.

Patient 6 (*J.R.F.*). A 94-year-old retired physician with rheumatoid and degenerative arthritis and a chronic brain syndrome secondary to generalized arteriosclerosis was transferred to this hospital from a nursing home. He had slight edema of both feet. His blood urea nitrogen was 19 mg./100 ml.

The patient was on an unrestricted sodium diet and his mild pedal edema remained, despite mercurial, chlorothiazide, and acetazoleamide diuretics. He was given spironolactone for six days, again with no effect on the edema. His mean daily 17-hydroxycorticosteroid, 17-ketosteroid, and aldosterone levels did not change significantly during the period of study (FIGURE 5).

Patient 7 (*A.S.*). A 68-year-old white male with an old thrombosis of the middle cerebral artery and a right hemiplegia was admitted for nursing care. He had a very mild pedal edema, which persisted despite mercurial and chlorothiazide diuretics. He was given spironolactone for five days without clinical response. The mean daily 17-hydroxycorticosteroid excretion was slightly lower and the mean 17-ketosteroid excretion was slightly higher while he was on spironolactone (FIGURE 5). This patient's aldosterone excretion tended to rise slightly during spironolactone therapy.

Comment. One patient with congestive heart failure who had failed to diurese with other agents lost 9 lb. on spironolactone. Spironolactone was administered together with an organomercurial and acetazoleamide to another patient with congestive heart failure, and this combination was four times more effective in its diuretic action than the latter two drugs alone. Two other patients with heart disease and very mild pedal edema did not lose their edema while on spironolactone. The edema of these two patients may well have been related more to senile tissue factors than to cardiac failure. Hill *et al.*,[19] Laragh,[14] and others have previously commented on factors other than adrenal steroids that may be involved in edema of cardiac origin.

	17-OHCS mg/24 hr.		17-KS mg/24 hr.		ALDOSTERONE µg/24 hr.	
	BEFORE	DURING	BEFORE	DURING	BEFORE	DURING
PT. 6	2.9	2.9	5.6	6.9	10.9	9.9
PT. 7	7.4	4.6	7.4	11.9	11.1	14.0

FIGURE 5. Mean five-day urinary steroid levels before and during spironolactone therapy in patients 6 and 7 with heart disease and edema, which did not respond to spironolactone.

Nephrotic Syndrome

Patient 8 (*W.M.J.*). A 39-year-old white male with poorly regulated diabetes mellitus of 18 years' duration was admitted to the hospital because of anasarca secondary to Kimmelstiel-Wilson's disease. In the few months prior to admission the patient had become very edematous and had failed to respond to mercurial, chlorothiazide, or acetazoleamide diuretics.

The response to spironolactone was as follows. The patient was placed on spironolactone, and a 2-lb. weight loss was noted during the first 24 hours. However, at this time he developed acute pulmonary edema and severe pneumonia involving all but the right lower lobe. He was treated with digitalis and antibiotics and after being critically ill for six days he began to improve. Although spironolactone was continued during the period of pneumonia, the patient lost very little weight, but with antibiotic therapy he began to diurese rapidly. Spironolactone was discontinued after 12 days of therapy, during which time he had lost 11 lb. However, his renal failure had continued to progress, he became uremic, lethargic, and disoriented, and his diabetes became very difficult to control. A pericardial friction rub developed, and his condition progressively deteriorated; he died 14 days later. Post-mortem examination revealed no evidence of toxicity to spironolactone.

Comment. This patient with diabetes and nephrosis lost 11 lb. during 12 days of spironolactone therapy. He lost no weight while critically ill with pneumonia. Although his blood urea nitrogen rose during therapy, it continued to rise after the drug was discontinued, and at autopsy his kidneys showed only intercapillary glomerulosclerosis.

Metastatic Carcinoma

Patient 9 (*R.A.*). A 52-year-old male with extensive metastatic carcinoma of the prostate was admitted to the hospital because of anemia and marked pedal edema. He had paralysis of both legs secondary to metastatic involvement of the spinal cord. During the two months prior to admission the patient had been confined to a wheel chair. However, despite change of position the pedal edema persisted, and in the mornings a mild periorbital edema had been present. He did not lose weight on mercurial diuretics.

The response to spironolactone was as follows. During treatment with spironolactone alone the patient lost only 1 lb. in six days, and there was no change in the edema. One cc. of meralluride was given on the seventh day of therapy, which was followed by a 4-lb. diuresis. Spironolactone was stopped on the tenth day of therapy, and the patient died 14 days later from causes unrelated to spironolactone therapy.

Comment. Spironolactone was used in combination with a mercurial diuretic to achieve diuresis in this patient with metastatic carcinoma. The marked dependent edema had not responded to meralluride alone. Death was apparently unrelated to spironolactone therapy, as post-mortem examination revealed no sign of toxicity to the drug. The autopsy did reveal an adenocarcinoma of the prostate with generalized metastases to bone, lymph nodes, and the left adrenal gland. The liver, kidneys, thyroid gland, and pituitary gland were normal on microscopic examination.

Idiopathic Edema

Patient 10 (*B.J.P.*). A 25-year-old white female was admitted to the hospital for evaluation of recurrent edema of 11 years' duration. On a diet containing 20 to 30 mEq. of sodium, she usually did not become edematous; however, marked edema developed when she was on a normal diet. Nine days prior to admission she was admitted to another hospital, where she gained from 85 to 114 lb. during three days on a regular diet. She failed to respond to mercurial diuretics and was transferred to this hospital for further studies. On numerous hospitalizations over the 11 years prior to admission the patient was never found to be hypertensive, nor was she found to have evidence of cardiovascular, hepatic, or renal disease. She was a small girl with a blood pressure of 100/60 mm. Hg, a pulse rate of 88/min., a respiratory rate of 22/min., and a normal temperature. She weighed 114 pounds and had generalized edema without ascites. The remaining results of physical examination were within normal limits. She had a normal phenolsulfonphthalein excretion, blood urea nitrogen level, Bromsulfalein retention, and serum albumin and globulin levels. A total eosinophil count was 228/cu. mm. Her serum sodium was 144 mEq. and potassium 4 mEq. per l., and serum calcium and phosphorus levels were also normal. With a diet containing 75 mEq. of sodium per day, her mean daily sodium excretion was approximately 60 mEq./24 hours and her mean potassium excretion also was 60 mEq./24 hours on three control days prior to therapy with spironolactone (FIGURE 6).

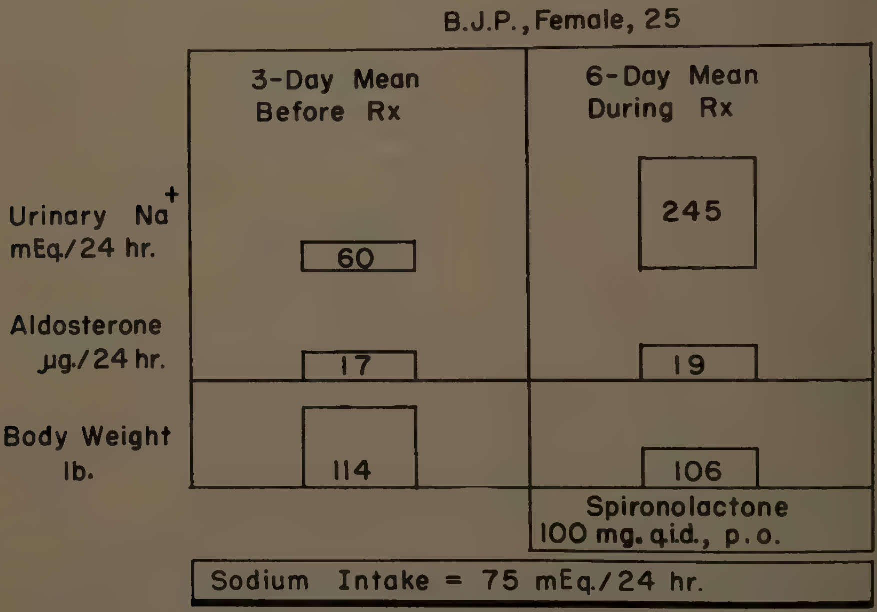

FIGURE 6. Effects of spironolactone on body weight and urinary sodium and aldosterone levels in patient 10 with edema of unknown origin.

Response to spironolactone: during six days of spironolactone therapy she lost 8 lb., or 7 per cent of her body weight. Her mean daily sodium excretion rose to approximately 250 mEq./l., and potassium fell to 40 mEq./l. during these six days of therapy. Mean aldosterone levels remained unchanged at 17 and 19 µg./24 hours before and during therapy respectively. There were no changes in urinary 17-hydroxycorticosteroid or 17-ketosteroid levels. There was no evidence of hematological, renal, hepatic, cutaneous, or neurological toxicity during spironolactone therapy.

Patient 11 (*O.L.M.*). A 43-year-old white housewife had recurrent edema for one year. Previous therapy with chlorothiazide had resulted in weight loss, which was always accompanied by weakness and muscle cramps. Without diuretic therapy her weight would increase from 130 to 140 lb. and she would have severe headaches. Extensive studies in the past revealed normal renal, hepatic, and cardiovascular function. On a diet containing 20 mEq. of sodium she continued to gain weight unless diuretics were administered. Her admission to the hospital was prompted by extreme weakness, which accompanied a four-day period of chlorothiazide therapy.

No abnormality was noted on physical examination except a mild edema. Her weight was 130½ lb. Her serum sodium was 140 and potassium was 3.3 mEq./l. Repeated studies of hepatic and renal functions showed them to be within normal limits. The patient was placed on a diet containing 1500 cal. and 50 mEq. of sodium, and her weight increased 6 lb. in six days. Her mean daily excretion of sodium was 3 mEq. and of potassium 22 mEq. per 24 hours (FIGURE 7).

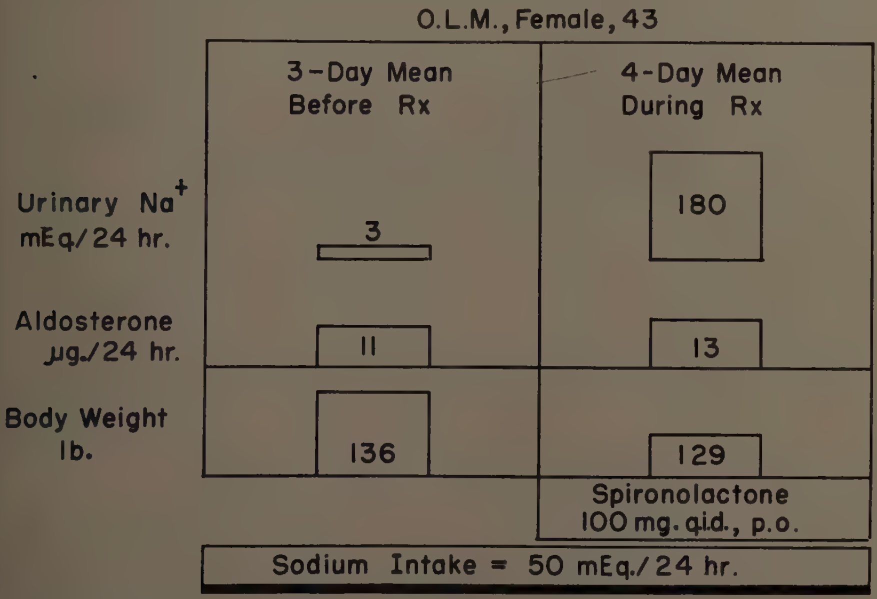

FIGURE 7. Effects of spironolactone on body weight and urinary sodium and aldosterone levels in patient 11 with edema of unknown origin.

The response to spironolactone was as follows. On the first day of spironolactone therapy, the patient's urinary sodium excretion increased to 230 mEq. and remained above 140 mEq. on the following two days. Her mean potassium excretion was 40 mEq./24 hours. No significant change was noted in the serum sodium level; however, the serum potassium level increased from 3.3 to 4.9 mEq./l. Urinary aldosterone levels were within the upper limits of normal, and no significant change was noted on or after spironolactone therapy. No change was noted in the urinary 17-hydroxycorticosteroid or 17-ketosteroid levels. On the fourth day of spironolactone therapy she developed a mild erythematous maculopapular rash and the drug was discontinued. Because of the patient's insistence that she had had this type of rash many times previously and because of her excellent response to spironolactone, the drug was later reinstituted with excellent clinical results and without recurrence of the rash. No other toxicity was noted.

Patient 12 (*G.F.*). A 51-year-old female, a registered nurse, was admitted to the hospital for evaluation of recurrent edema of unknown etiology. Minimal episodic edema had been noticed for 20 years, but during the past two years there had been marked exacerbation of both the degree and the duration of the edema. She required almost constant diuretic therapy to maintain normal weight. She had noted that the edema usually subsided on 3 or 4 days of bed rest but returned when she resumed normal daily activity. In addition, overnight bed rest usually decreased the pedal but increased the periorbital edema. The patient had been extensively studied in several medical centers, but no cause for the edema had ever been determined. She had preeclampsia with each of her three children, born in 1934, 1936, and 1941. She had had no hypertension or proteinuria before, between, or after these three pregnancies. She had a lower urinary tract infection 9 years prior to admission, but there was no other history of renal disease.

She was a well-developed well-nourished edematous white female in no acute distress. She had a blood pressure of 110/70 mm. Hg bilaterally, a pulse rate of 88/min., a respiratory rate of 18/min., and her temperature was normal. The remainder of the physical examination was normal except for mild periorbital edema, 3+ pitting pedal edema, and 2+ pretibial edema of both lower extremities.

Complete blood count and urinalysis were normal. Twenty-four-hour urine protein determinations were negative on several occasions. During a Fishberg concentration test her urine was concentrated to a specific gravity of 1.028, and phenolsulfonphthalein excretion was normal. Serological test for syphilis was negative. Bromsulfalein retention was 4 per cent in 45 min., and serum bilirubin, total protein, alkaline phosphatase, and thymol turbidity levels were normal. Blood urea nitrogen, fasting blood sugar, serum sodium, potassium, calcium, and phosphorus levels were all normal. The patient was placed on a diet containing 75 mEq. of sodium per 24 hours. For the first five days of hospitalization the patient was allowed up and about the ward with her usual activity, during which time she had a slightly positive sodium balance with an increase in her weight from 142 to 144 lb. (FIGURE 8). On the fifth day she was placed on absolute bed rest, and her weight rapidly decreased over a five-day period to 138 lb. During this period of complete rest there was a marked natriuresis without significant change in urinary potassium excretion. The urinary aldosterone levels were relatively unchanged. No change was noted in the urinary 17-hydroxycorticosteroid or 17-ketosteroid levels. On the tenth day she was placed on forced ambulation, with as much walking as she could comfortably tolerate. Her urinary aldosterone levels rose to the abnormal high of 38 μg./24 hours, sodium excretion decreased to 4 mEq./24 hours, and she gained 6 lb. in the first 48 hours of forced ambulation. Forced ambulation was continued and on the thirteenth day of hospitalization spironolactone therapy was started.

The response to spironolactone was as follows. Sodium excretion rose on the first day of spironolactone therapy to 105 mEq. and on the second day to 151 mEq. per 24 hours. Urinary potassium levels fell to approximately 54 mEq./24 hours. She lost 4 lb. and her edema almost disappeared. No pretibial edema was noted. No change was noted in the urinary 17-hydroxycorticosteroid levels. The 17-ketosteroid levels increased slightly on spironolactone therapy. She has been able to maintain her usual daily activities without recurrence of significant edema on continued spironolactone therapy.

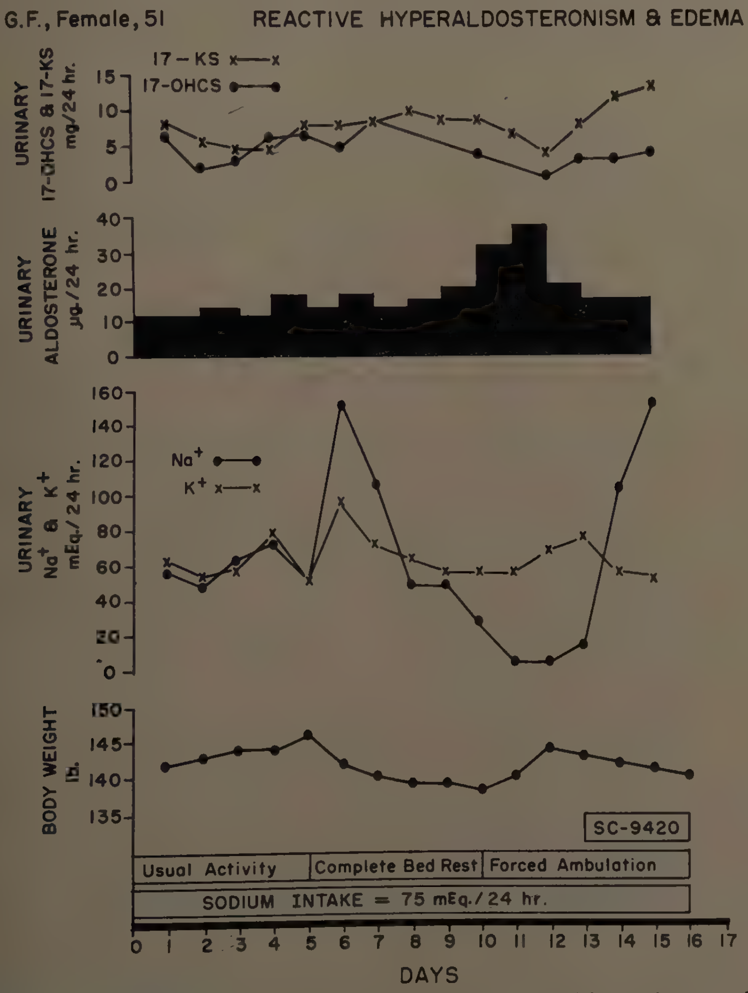

FIGURE 8. Metabolic effects of spironolactone in patient 12 with reactive or orthostatic edema and hyperaldosteronism.

Comment. In all 3 patients with "idiopathic edema," spironolactone administration was accompanied by weight loss and negative sodium balance. Only patient 12, with orthostatic or reactive edema and hyperaldosteronism, had unequivocally elevated urinary aldosterone levels. The marked response to spironolactone in patients 10 and 11 suggests that aldosterone was important in the production or maintenance of their edema, although their urinary aldosterone levels were only slightly higher than the normal mean. These 2 patients may represent a relative hyperaldosteronism similar to the three patients in whom Luetscher and Lieberman demonstrated failure of the depression of aldosterone output after sodium loading.[12]

DISCUSSION

The role of spironolactone as an aldosterone antagonist has been clearly shown. The present studies emphasize the usefulness of this compound in treating patients who either fail to diurese on other regimens or whose diuresis is accompanied by undesirable side effects. They further indicate that spironolactone may be useful in studying the mechanisms of edema formation in some patients.

Weight loss and natriuresis were obtained by spironolactone therapy in patients with cirrhosis, congestive heart failure, nephrosis, idiopathic edema, and edema secondary to metastatic carcinoma. The failure to diurese on spironolactone therapy, noted in one patient with cirrhosis, was probably related to circulatory collapse. Although this patient died two weeks after therapy, her death was apparently due to cirrhosis and was unrelated to the spironolactone treatment. Two of the 4 patients with arteriosclerotic heart disease who did not diurese had very mild pedal edema and no significant congestive heart failure. All of the other patients had significant diuresis on spironolactone therapy, although 2 patients, Nos. 5 and 9, had a much greater diuresis when other diuretics were added. In patient 5, the addition of a third diuretic further enhanced the diuresis. Although none of these patients had marked hypokalemia during treatment with other diuretics, patients 11 and 12 became quite weak after chlorothiazide diuresis, and patient 11 had a serum potassium level of 3.3 mEq./l. Neither weakness nor hypokalemia was observed to follow diuresis induced by spironolactone.

The possible usefulness of spironolactone in studying mechanisms of edema formation is illustrated by patients 10, 11, and 12, for whom the clinical diagnosis was idiopathic edema. That aldosterone was of importance in the production or maintenance of edema in these patients is suggested by their marked response to spironolactone administration. The fact that the urinary aldosterone levels were only slightly higher than the normal mean for the sodium intake in each patient further suggests that these patients had a "relative hyperaldosteronism." The reactive or orthostatic edema and hyperaldosteronism in patient 12 is the subject of another report.[30]

That spironolactone does not significantly decrease adrenal cortical steroidogenesis has been demonstrated by the lack of a consistent change in either 17-hydroxycorticosteroid or aldosterone excretion in patients receiving this compound. This is further evidence of a peripheral antagonistic effect of spironolactone on aldosterone action. A compensatory increase in urinary aldosterone levels as a result of spironolactone therapy was anticipated more frequently than the occasional increase that was actually observed. The slight rise in urinary 17-ketosteroid excretion noted in some patients on spironolactone therapy may be an artifact. Powdered SC-8109 and SC-9420 give color with metadinitrobenzene, which could lead to falsely high 17-ketosteroid levels.

The only toxicity noted was a rash that occurred in patients 5 and 11 and that subsided quickly on withdrawal of the drug. The rash in patient 11 may not have been related to the drug. Drowsiness and other signs of central nervous system toxicity were not observed in any of these patients. This may have been related to the relatively low dose used. There was no rise in blood ammonia levels in two patients with cirrhosis of the liver during therapy, although chlorothiazide treatment had induced signs of impending hepatic failure on previous occasions. There was no evidence of hepatic, gastrointestinal, renal, or other toxicity, either clinically or at post-mortem examination, that could be attributed to spironolactone. Patient 1 received 24 gm. of spironolactone over a period of 6 months with repeated diuresis and no sign of toxicity.

SUMMARY

Fourteen metabolic studies were made on 12 patients who received the spirolactone SC 9420 (spironolactone) orally for 3 to 12 days. All patients had ascites or edema or both, and a satisfactory diuresis could not be obtained with other diuretics.

On spironolactone therapy patients with cirrhosis, nephrosis, congestive heart failure, idiopathic edema, and severe edema secondary to metastatic carcinoma had significant weight loss and sodium and water diuresis. Seven of the 12 patients diuresed satisfactorily on spironolactone alone. Natriuresis was accompanied by either a decrease or no change in potassium excretion. Two patients who responded minimally to spironolactone therapy alone responded quite well when a mercurial diuretic and acetazoleamide were added. Both patients had previously failed to respond satisfactorily to the other diuretics alone. Three patients failed to respond on spironolactone alone. Two of these had minimal edema secondary to arteriosclerotic heart disease, and one was critically ill with repeated episodes of circulatory collapse. There was no clinical or pathological evidence of hematological, renal, or hepatic toxicity. Neither drowsiness nor other signs of neurological toxicity were observed in any patient. Two patients developed maculopapular skin rashes: 1 mild and the other moderately severe. The patient with the mild rash was given spironolactone again without recurrence of the rash. The present studies indicate that spironolactone may be useful both in diuretic therapy and in the investigation of the role of aldosterone in edema formation.

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THE USE OF DIURETICS IN THE PREGNANT PATIENT

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The pregnant female affords the obstetrician many interesting physiological problems. Not the least among these is the problem of sodium and water retention.[1] The role of sodium retention as an important factor in the production of edema of pregnancy and subsequently in the development of preeclampsia has long been recognized. The magnitude of this problem can best be highlighted by stating that according to the National Office of Vital Statistics[2] toxemia of pregnancy was still the leading cause of maternal death in the United States in 1957 (the latest year surveyed), accounting for 472 deaths. The general incidence of toxemia of pregnancy is approximately 10 per cent.

Although the etiology of preeclampsia is still little understood, the physiopathological disturbances produced by this syndrome are fairly clear and result clinically in a characteristic triad of signs manifested by edema, hypertension, and albuminuria. Two factors mediating this situation are: (1) generalized arteriolar constriction, and (2) derangement of sodium and water metabolism. The tendency of pregnant women to retain sodium is greatly enhanced by the marked elevation of estrogen and adrenocorticosteroids during pregnancy. This derangement of salt and water metabolism is further aggravated either by excessive salt intake or by excessive production of adrenocorticosteroids resulting in sodium retention.[3] The cornerstone of good prenatal care in the prevention and treatment of toxemia of pregnancy is control of ionic sodium, first by sodium restriction in the prenatal diet and, second, when edema and weight gain become evident, by elimination of sodium from the extracellular tissue compartment. The treatment of toxemia of pregnancy is of necessity symptomatic; hence the management of edema with or without toxemia requires the use of agents that will promote excretion of sodium and water with the improvement of urinary function and preservation of electrolyte balance.

Measures to promote diuresis begin with bed rest and sedation, measures that aid in the reduction of arteriolar spasm, leading often to improvement in renal flow and glomerular filtration. Next, an increase in fluid intake, orally and intravenously, are advocated for diuresis. The administration of 3000 cc. or more of 5 per cent glucose in water may effectively decrease hemoconcentration and favor better glomerular filtration. Finally, chemical agents have been employed for diuresis with varying degrees of success until recent years.

The drugs most commonly used until recently fall into four categories:

(1) The acidifying salts, for example, ammonium chloride. These agents are frequently ineffectual and require long periods of therapy to achieve the acidosis necessary to produce sodium loss.

(2) The organomercurial drugs. These drugs are potent and reliable diuretics that depress the tubular mechanism of reabsorption. They have found little popularity in obstetrics in the treatment of preeclamptic edema because of the potential hazard of adding to the pathological changes in the kidneys

produced by toxemia, the characteristic poisoning effect of the mercuric ion. The toxicity of this drug in a severe preeclamptic or eclamptic patient is another contraindication to its use.

(3) The important and popular carbonic anhydrase inhibitors, for example, acetazolamide. This drug produces diuresis by depressing tubular reabsorption of bicarbonate ion by the inhibition of carbonic anhydrase. There is a loss of sodium along with bicarbonate and potassium and a retention of chlorides with consequent acidosis.

(4) Finally, the diuretics of the benzothiadiazine group, which have emerged as extremely efficacious drugs in the elimination of sodium and water without the production of acidosis or hypokalemia. This latter group is of great interest to the obstetrician.

The purpose of this paper is to present an evaluation of the effectiveness of the benzothiadiazine drugs, chlorothiazide, hydrochlorothiazide, flumethiazide, and benzydroflumethiazide in the management of edema of pregnancy and preeclampsia. The pharmacological effect of these drugs is similar, the selective inhibition of reabsorption of sodium and chloride by the renal tubule producing the excretion of sodium and chloride in almost equal proportions without significant loss of bicarbonate. Potassium is excreted to a much lesser degree. Consequently metabolic acidosis is no problem and sodium loss is the most desirable feature of this mechanism.

Methods and Materials

Clinical studies and observations were made of 315 pregnant women in the Prenatal Clinic of the New York Medical College–Metropolitan Medical Center. Only patients with objective evidence of fluid retention, such as abnormal, sudden weight gain or varying degrees of pitting edema, with or without hypertension, were selected. In this group 269 women were evaluated only on an outpatient basis. Ninety-two of these patients manifested toxemia of pregnancy, using the following criteria for diagnosis: (1) hypertension above 144 mm. systolic and/or 90 mm. diastolic; (2) edema; and (3) proteinuria.

Patients were advised to continue the customary prenatal diet and were told to avoid excessive salt intake rather than salt restriction. Fluids were permitted ad libitum. One of the following drugs was then prescribed: (1) chlorothiazide, one 500-mg. tablet in the morning and one 500-mg. tablet at night, totaling 1000 mg. daily; (2) hydrochlorothiazide, one 50-mg. tablet in the morning and one 50-mg. tablet at night, totaling 100 mg. daily; (3) flumethiazide, one 500-mg. tablet in the morning and one 500-mg. at night, totaling 1000 mg. daily; or (4) benzydroflumethiazide, one 5-mg. tablet in the morning and one 5-mg. at night, totaling 10 mg. daily.

Notations of blood pressure, weight, edema, proteinuria, and subjective reactions to the drug were made at weekly intervals throughout the course of the investigation.

The remaining 46 women in this study were admitted to the hospital because of severe toxemia of pregnancy. Closer observations of urinary excretion rates, serum electrolytes, and blood chemistries were possible in this group.

Results

The response in the outpatient group of 269 women is shown in TABLE 1.

Weight loss. In all patients weight loss was evaluated at the end of the first week of continuous therapy. The average weight loss was greatest with chlorothiazide, the maximum being 16 lb. Hydrochlorothiazide and flumethiazide followed in order of potency. However, both drugs clearly manifested excellent diuretic response and in individual cases there were losses of up to 10 and 12 lb. in one week. The group receiving benzydroflumethiazide must be evaluated in a somewhat different light. Patients in this group were selected more for hypertension than because of edema and weight gain.

Weight gain (*rebound*). When medication was discontinued for one week after initial therapy, a rebound phenomenon was invariably noted, and most patients regained more than the initial weight loss. The extreme example of this was a patient who lost 9 lb. in four days on chlorothiazide and regained 12.75 lb. in the week after discontinuing the drug. When the drug was administered continuously, rebound occurred much less frequently and was less marked.

TABLE 1

RESPONSE TO VARIOUS DIURETICS IN 269 PREGNANT WOMEN WITH EDEMA OR TOXEMIA

No. of cases	Diuretic agent	Wt. loss in 1st wk. (av.) (lb.)	Edema		Blood pressure			Toxic reactions			Rebound
			Decreased	Unchanged	Decreased	Unchanged	Elevated	None	Mild	Severe	Weight gain (lb.)
102	Chlorothiazide (500 mg. b.i.d.)	5.16	84	18	20	72	10	77	21	4	6.30
67	Hydrochlorothiazide (50 mg. b.i.d.)	4.21	41	26	19	33	15	51	13	3	6.35
66	Flumethiazide (500 mg. b.i.d.)	3.54	54	12	18	44	4	53	9	0	4.84
32	Benzydroflumethiazide (5 mg. b.i.d.)	3.21	13	19	9	15	6	27	6	0	6.33

Toxic reactions. Only 66 patients developed reactions attributed to the drugs. Of these 59 were mild and 7 severe enough to discontinue medication. The usual reactions were nausea, vomiting, dizziness or lightheadedness, drowsiness, weakness, and one case of pruritus with a faint rash.

Blood pressure. The blood pressure responses with all of the drugs was inconsistent and showed no specific trend. A drop or rise of 10 mm. Hg was accepted as a change.

Duration of treatment. One hundred and sixty-two patients were on continuous medication for more than two weeks. The longest continuous therapy was 1000 mg. of chlorothiazide daily for 17 weeks. Approximately 85 per cent of the patients on prolonged treatment maintained their weight within 3 lb. after the initial loss, or gained thereafter at the normal expected rate.

TABLE 2

THE HOURLY URINARY EXCRETION OF TOXEMIC PATIENTS WITH OLIGURIA AND/OR MARKED EDEMA IN RESPONSE TO INTRAVENOUS ADMINISTRATION OF VARIOUS DIURETICS

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
hourly urinary output with I.V. chlorothiazide 500 mg.																								
C.T., eclampsia	40	32	20	18	10	5	100	114	115	40	58	67	53	60	50	75	55	70	160	120	200	160	180	180
D.V., preeclampsia	95	70	70	65	40	45	400	500	300	400	200	150	150	300	200	200	300	100	350	400	300	250	210	180
A.P., preeclampsia	70	60	65	75	75	75	400	500	500	310	200	300	250	150	260	290	100	200	500	600	250	40	30	40
A.W., preeclampsia	44	45	45	50	50	100	35	185	350	350	150	280	350	75	75	50	50	100	100	100	200	200	250	250
M.H., preeclampsia	100	50	30	40	30	175	50	200	400	200	300	200	350	200	100	50	50	50	50	50				
hourly output with I.V. hydrochlorothiazide 50 mg.																								
L.G., preeclampsia	50	30	15	15	20	60	350	400	250	300	200	100	50	50	100	100	50	40	130	250	110	145	30	50
C.V., preeclampsia	80	40	60	20	40	30	500	300	200	200	300	150	300	200	300	100	250	200	50	150	200	300	500	200
M.C., preeclampsia	50	50	50	100	50	50	50	100	150	100	150	100	120	150	100	50	100	75	100	300	100	200	100	200
L.H., preeclampsia	70	40	0	40	55	50	50	100	150	150	100	200	150	300	300	675	300	300	300	100	200	50	50	50
hourly output with I.V. flumethiazide 500 mg.																								
M.S., preeclampsia	100	150	100	100	50	50	100	100	600	300	100	450	400	200	250	50	20	70	100					
M.V., preeclampsia	100	100	150	100	100	100	800	300	100	150	100	50	100	100	100	50	50	50	50	150	200	350	400	100
J.H., preeclampsia	125	150	150	210	50	20	50	60	100	300	250	180	270	200	175	125	100	100	250	100	350	175	125	175

Toxemia Group

There were 92 toxemias of pregnancy in the group. Thirty-three patients manifested a drop in blood pressure, 30 were unchanged, and 29 showed an actual rise in blood pressure during treatment. The best effect on hypertension was produced by benzydroflumethiazide, 9 cases of 26 patients with toxemia showing a drop in blood pressure, four showing a rise, and 13 cases remaining unchanged.

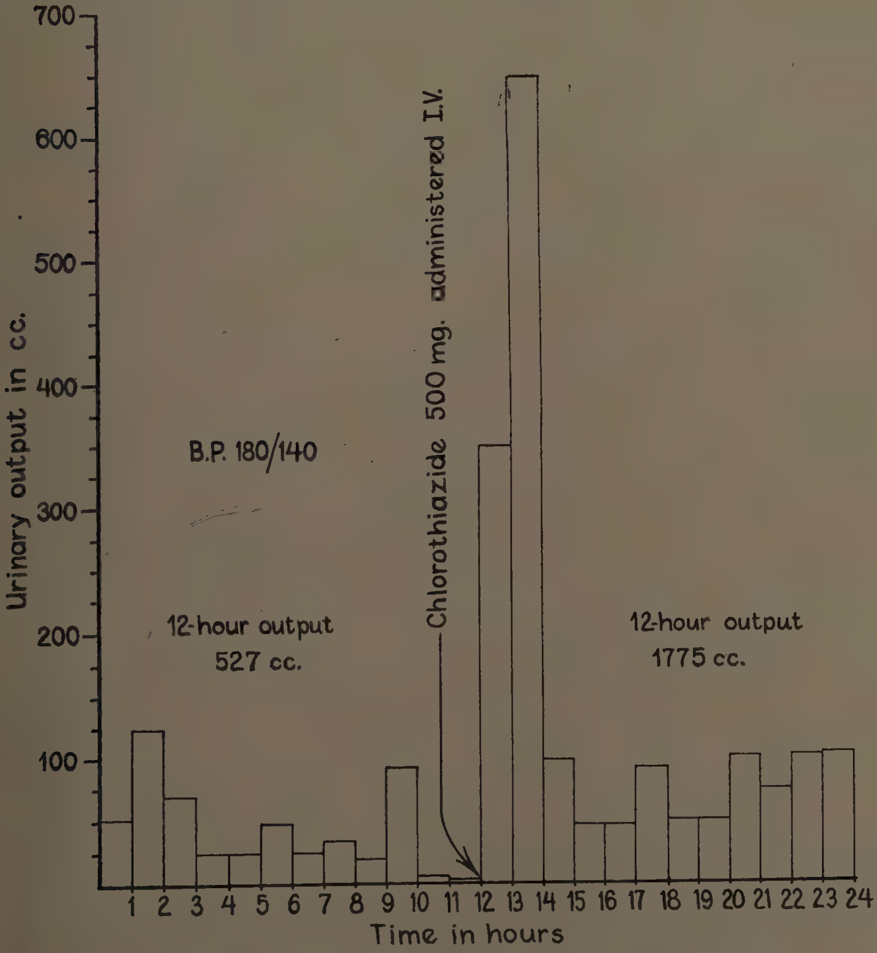

FIGURE 1. Response to I.V. chlorothiazide in preeclamptic patient, M.A.

Intravenous Therapy

Forty-six patients were admitted because of severe toxemia. This group was placed at bed rest with minimal sedation (phenobarbital 60 to 90 mg. three times each day), nothing by mouth for at least 24 hours, intravenous fluids of 5 per cent glucose in distilled water, 3000 cc. daily, and a Foley catheter inserted into the bladder to measure hourly urinary output. After a control period of 6 to 24 hours, chlorothiazide, 500 mg., hydrochlorothiazide, 50 mg., or flumethiazide, 500 mg., was administered intravenously. Usually two doses at 12 hour intervals were administered. Subsequently the patient was placed on oral therapy in the dosage outlined above.

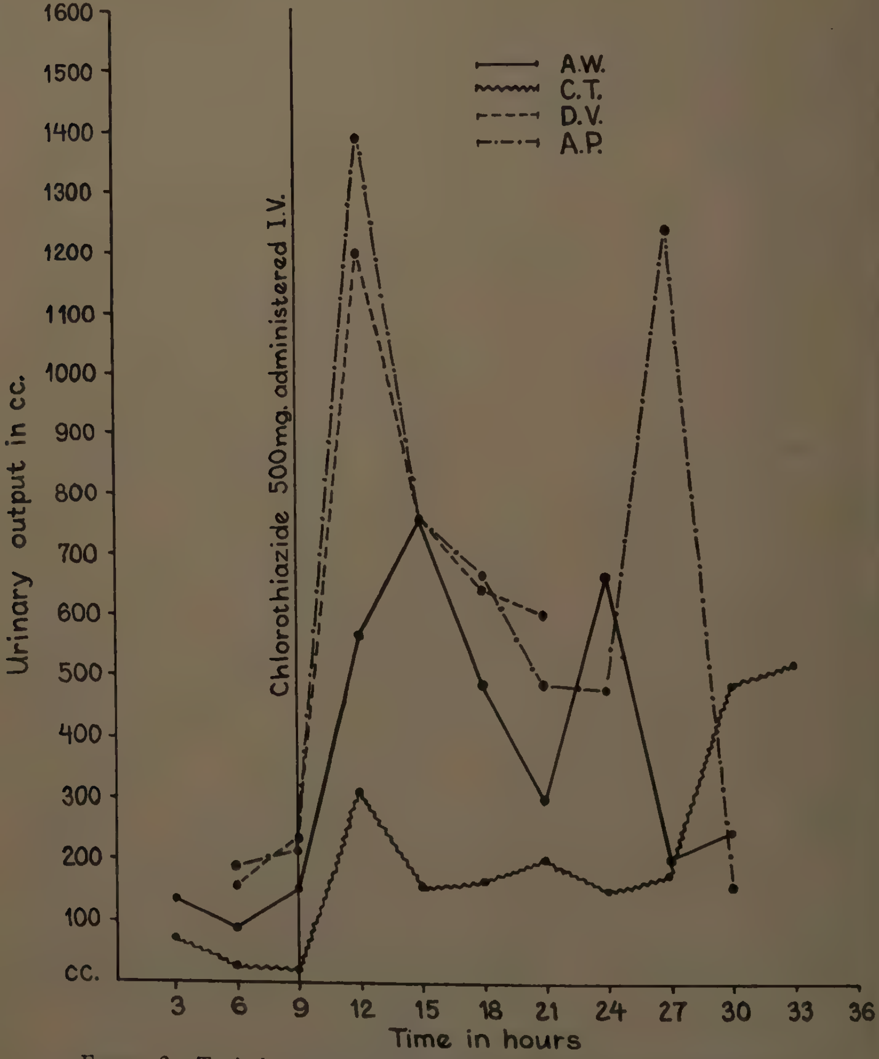

FIGURE 2. Typical response to I.V. chlorothiazide in preeclamptic patients.

Results

The urinary output was universally increased approximately fivefold (TABLE 2). There was a uniform sharp increase in hourly output in the first hour of

TABLE 3

SERUM ELECTROLYTE STUDIES, BLOOD CHEMICAL CHANGES AND FLUID LOSS IN A PREECLAMPTIC PATIENT*

Day	1	2	3	4	5	6	7	8	9	10	11	15	17
Na	129			120			118				114	121	128
K	3.8			3.9			4.9				3.4	4.5	3.6
Cl	116			108			97				96	114	108
CO_2	46			40			37				42	48	60
Uric acid	2.8			2.6			4.1				3.2	6.7	3.4
Weight	146.5			140			139				137.5	130	119
Blood pressure	150/100	138/90	138/88	130/90			124/70				120/70	Del.	110/90
Hydrochlorothiazide	100 mg. I.V.	100 oral	100 oral	100 oral	100 oral	100 oral	100 oral	100 oral	100 oral	100 oral	100 oral	Disc.	Disc.

* Patient L.G.

five times the previous average hourly output, reaching a peak in 2 to 4 hours and then gradually decreasing, but remaining at a higher level than before treatment. FIGURE 1 represents the typical response of a severe preeclamptic patient developing a severe oliguria whose urinary output in the last 6-hour period was 175 cc. The blood pressure was 180/140, the urine showed four plus albumin, and she was markedly edematous. She was given 500 mg. of chlorothiazide intravenously in 250 cc. of 5 per cent glucose in distilled water, and in one hour her output rose from 2 cc. to 350 cc. In the second hour it rose to 650 cc. and continued to improve thereafter. FIGURE 2 illustrates a small group of responses that typify the entire group. Total urinary output rose remarkably in almost all cases, frequently exceeding 5000 cc. in the first 24-hour period. Weight loss was marked and rapid; in one case weight loss was 8 lb. in the first day. Urinary output exceeded fluid intake for 5 or more days and then reached an equalizing level. This usually reflected the patient's state of hydration. When this point was reached, weight loss ceased.

TABLE 4
SERUM ELECTROLYTE STUDIES, BLOOD CHEMICAL CHANGES, FLUID LOSS IN A PREECLAMPTIC PATIENT*

Day	1	2	3	4	5	6
Na	129.4				131	137
K					4.8	5.1
Cl	107				112	98
CO_2	42				48	48
Uric acid	2.7				3.5	
Weight	183 lbs.	179	177	174	Del.	P.P.
Blood pressure	186/110	162/110	150/100	152/100	120/90	132/90
Chlorothiazide	1000 mg. I.V.	1000 mg. oral	1000 mg. oral	1000 mg. oral	Disc.	Disc.

* Patient D.V.

TABLE 5
SERUM ELECTROLYTE STUDIES, BLOOD CHEMICAL CHANGES, FLUID LOSS IN A PREECLAMPTIC PATIENT*

Day	1	2	3	4	5
Na	126				128
K	4.0				4.3
Cl	106		110		107
CO_2	32				
Uric acid	2.4		3.8		3.8
Weight	139.5	135	133		130
Blood pressure	130/90	120/80	130/80		120/80
Flumethiazide	1000 mg. I.V.	1000 mg. oral	1000 mg. oral	1000 mg. oral	1000 mg. oral

* Patient M.V.

Serum electrolyte studies revealed that sodium levels fell in approximately 30 per cent of cases, potassium in 18 per cent, and chlorides in 6.5 per cent in those cases in which therapy was continued for longer than 7 days (TABLES

3, 4, and 5). There was no clinical evidence of hypokalemia or hyponatremia in any patient in this study.

Comments

The retention of sodium in the interstitial fluid compartment in pregnant women is recognized as one of the most constant factors in the development of preeclampsia. Thus any drug that can effectively and safely mobilize and eliminate salt and water in pregnant women is a most useful and desirable agent. Our experiences indicate that the benzodiathiazine derivatives are both potent in effecting diuresis and safe to mother and child.

The constancy and predictability of weight loss and reduction of edema is most impressive. The degree of response is almost in direct ratio to edema and sodium retention.

Aside from minor reactions, it was found that there were no harmful clinical effects in terms of salt or potassium depletion syndromes. This "safety valve" effect is probably related to a decreasing ability of the benzodiathiazine drugs to cause sodium excretion as the excess of sodium is being eliminated from the interstitial compartment.[4]

In the treatment of toxemia of pregnancy the effect of these drugs on blood pressure seems to be a secondary result of sodium excretion and fluid loss. The most interesting and important effect of the benzothiadiazine drugs in the treatment of severe preeclampsia is their ability to mobilize sodium and dramatically improve urinary output in the presence of marked oliguria. This remarkable faculty in the presence of varying degrees of kidney damage represents a unique advance in therapy of the toxemia patient. The intravenous use of these agents offers a newer modality in the treatment of the critically ill patient with toxemia of pregnancy.

Summary

Three hundred and fifteen pregnant women with edema or toxemia were treated with the benzodiathiazine drugs.

These drugs are effective in achieving rapid weight loss and decrease in edema.

Toxic reactions occurred in 66 patients but were severe in only 7 cases.

There were no definite specific hypotensive effects attributable to these drugs in the treatment of toxemia of pregnancy.

A group of 46 patients with toxemia were treated intravenously with chlorothiazide, hydrochlorothiazide, and flumethiazide with dramatic diuretic response and weight loss.

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USE OF DIURETICS IN THE TREATMENT OF KIDNEY DISEASES*

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This paper will be limited to the presentation of results obtained during administration of newer diuretics to 13 patients with nephrotic syndrome of various origins and to some aspects of the management of such patients. We shall not discuss the use of diuretics in the treatment of edema associated with severe chronic renal failure or with acute glomerulonephritis (Ellis, Type 1),[6] since the latter most often appears to be secondary either to cardiac failure[6,19] or to an excessive salt and water intake in presence of severe oliguria.

The aim in the treatment of nephrotic syndrome is twofold: first, the cessation of proteinuria with subsequent correction of hypoproteinemia, hypoalbuminemia, hypercholesterolemia, and hyperlipemia; and, second, if the first cannot be accomplished, complete relief of edema with increase in well-being and working capacity. In working toward the primary aim, the use of corticosteroids, first employed in 1950,[7,14,23] is indicated in most cases. Precise knowledge of the underlying renal lesion is essential. In all patients whose history and clinical examination do not give enough diagnostic certainty as to the causal pathological lesion, percutaneous renal biopsies should be done by a well-trained and careful physician.

The risks involved are, we believe, warranted in view of the great advantages both to patients and to treating physicians. TABLE 1 outlines a list of the causes most frequently responsible for the nephrotic syndrome and its frequency, based on the findings of Kark and his collaborators[12] and of Berman and Schreiner.[1] Although some workers still advise the same steroid treatment for all patients with nephrotic syndrome, it seems quite obvious that the use of corticosteroids is contraindicated in the nephrotic syndrome secondary to diabetic nephropathy and would be of little or no benefit in cases secondary to multiple myeloma, amyloid disease, constricting pericarditis, or renal vein thrombosis.

When cessation of proteinuria is not obtained by one or two courses of corticosteroids (for 15 to 30 days each), diuretics are indicated for relief of edema. This aim was rarely achieved with the previous diuretics, such as ammonium chloride, urea, xanthine derivatives, acetazoleamide, aminometradine, amisometradine, and mercurial diuretics. Generally, the latter have not been used extensively in the treatment of nephrotic syndrome because of reports in the literature of nephrotic edema occurring during prolonged administration of mercurial compounds, including organic mercurial diuretics, to patients with edema.[16,24]

Since 1957, several new natriuretic drugs have been synthesized and found very potent. The compounds we have studied in our series are chiefly spironolactone,[3] chlorothiazide,[17,22a,b] hydrochlorothiazide,[5,21] and chlorthalidone (a phthalimidine or sulfamylated isoindoline derivative).[10]

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As shown in TABLE 2, the presence of aldosterone or a mineralocorticoid replacement, such as desoxycorticosterone, is necessary for the natriuretic activity of spironolactone, the mode of action of which is one of blocking aldosterone effects on the distal tubular reabsorption of sodium.[11,13] The natriuresis caused by the administration of chlorothiazide is due to a decrease in the proximal tubular reabsorption of sodium and of partial inhibition of the carbonic anhydrase in the distal tubules.[22a,b] One of the merits of chlorothiazide, and presumably of its derivatives, is its efficacy over a wide range of glomerular filtration rate (measured by inulin clearance) from 30 to 160 ml./min./1.73 sq. m. of surface area, as was previously shown.[2]

TABLE 1
NEPHROTIC SYNDROME

Causes	Frequency	
	98 patients*	45 patients†
I. Intrinsic renal lesions	57	31
Membranous and/or proliferative glomerulonephritis	(46)	
Tubular degeneration without glomerular changes	(11)	
II. Systemic diseases	36	11
Amyloidosis	(3)	
Disseminated lupus erythematosus	(18)	
Diabetic nephropathy	(15)	
Multiple myeloma		
III. Severe obstruction to renal venous flow	4	
Renal vein or inferior vena cava thrombosis		
Constrictive pericarditis		
IV. Miscellaneous	1	3

* All by renal biopsies. After Kark *et al.*[12]
† Thirty-six by biopsy, 9 by autopsy. After Berman and Schreiner.[1]

TABLE 2
SPIRONOLACTONE*
(Aldosterone-antagonist SC-9420)

	Natriuresis during spironolactone administration
In edematous states with hyperaldosteronism	Yes
In Addisonian patients on high sodium diet alone	No
In Addisonian patients on DOCA plus sodium diet	Yes
In adrenalectomized animals on high sodium diet plus glucocorticoid	No
In normal subjects on high sodium diet	No
In normal subjects on low sodium diet	Yes
Does not block aldosterone secretion	
Produces negative sodium balance in primary aldosteronism	

* Aldactone.

Our data are limited to the study of 13 patients with nephrotic edema. Two cases were due to diabetic nephropathy and 11 were due to intrinsic renal diseases. The latter group includes 8 patients with membranous glomerulonephritis, 1 with mixed proliferative and membranous glomerulonephritis, and 2 without evidence of glomerular lesion with the light microscope. Etiological diagnosis was obtained in 8 patients by percutaneous renal biopsy. Clinical diagnosis of nephrotic syndrome was based on the presence of edema, proteinuria above 3 gm./day, presence of doubly refractile and oval fat bodies in urinary sediments, hypoalbuminemia, hypoproteinemia, and hyperchloesterolemia.

Investigation of each patient with the nephrotic syndrome included detailed history and careful physical examination, repeated determinations of serum sodium, chloride, potassium, proteins, electrophoretic pattern, cholesterol, and total lipids, frequent measurements of renal function by phenolsulfonphthalein excretion, urea and creatinine clearances, urinary aldosterone,[18] and free and conjugated 17-hydroxycorticosteroids.[20] Each patient was on a fixed calculated protein, sodium, and potassium intake, and had daily urinary determinations of sodium, potassium, and proteins.

The use of the newer natriuretic agents alone or in combination was effective in relieving completely the edema in 12 of the 13 patients studied. The 13th patient admitted to the hospital in anasarca was discharged with only a slight amount of pleural effusion and without noticeable subcutaneous edema. The following detailed presentation of 7 patients provides more information on the effects of these newer diuretics in the nephrotic syndrome.

The first case to be discussed is that of a 57-year-old man with a generalized pitting edema, right pleural effusion, and ascites. Histological lesions of membranous glomerulonephritis and of pyelonephritis were found on percutaneous renal biopsy. Results of the sodium metabolic balance and of the effects of chlorothiazide and dexamethasone are shown in FIGURE 1. Complete disappearance of the generalized edema was achieved by administration of chlorothiazide at 2 gm./day for three weeks, with a very marked natriuresis apparently enhanced on at least two occasions by addition of meralluride. Subsequent administration of dexamethasone at 4 mg./day for 10 days was followed by complete cessation of proteinuria with correction of other biochemical abnormalities. This total remission has now persisted for two years, and is a "dream-response" for all concerned.

The combined effects of spironolactone and a thiazide derivative, P-1393, are illustrated in the second patient, a 48-year-old woman with nephrotic syndrome secondary to diabetic nephropathy (FIGURE 2). This patient was admitted in the spring of 1959 in anasarca, pulmonary edema, orthopnea, and hepatomegaly. She was known to have had hypertension and diabetes since 1955. Her renal function was poor, as measured by the phenolsulfonphthalein excretion of 2 per cent in 15 min. and of 14 per cent in 45 min., by the endogenous creatinine clearance varying between 12 and 35 ml./min./1.73 sq. m. of surface area, and by a blood urea at 70 mg. per cent. After a stormy first few days during which the patient's condition was critical and urine collections were inaccurate, she improved sufficiently to be placed on a fixed diet containing 20 mEq. of sodium per day. During administration of a thiazide derivative, P-1393, the patient showed a slight negative sodium balance with little change in weight. Addition of spironolactone at 600 mg./day for one week greatly enhanced the natriuresis, which persisted for eight days following cessation of the drug. Edema disappeared completely after a weight loss of 10 kg.

Spironolactone was studied in a third patient, aged 29, in whom histological examination of the percutaneous renal biopsy failed to reveal any glomerular lesion with the light microscope. The administration of this aldosterone-antagonist was accompanied by a significant decrease both in systolic and diastolic blood pressures, a total disappearance of proteinuria, and an increase

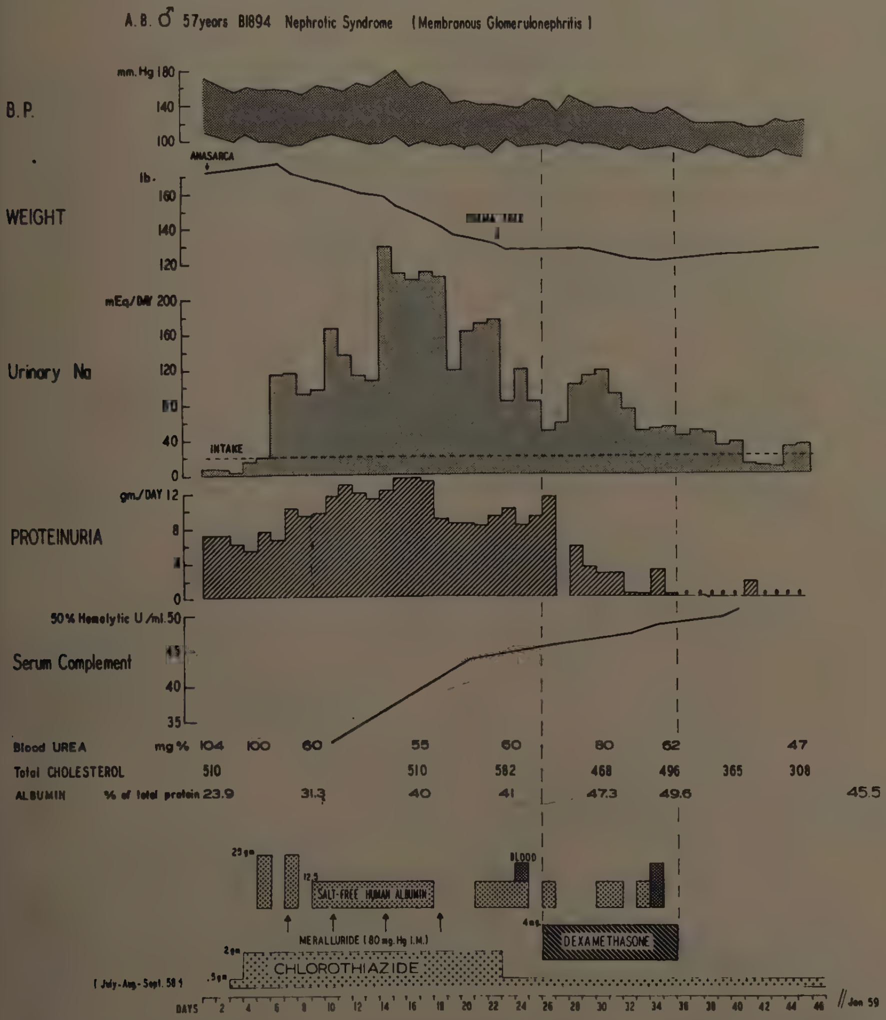

Figure 1. Patient A.B. Note the progressive fall in blood pressure during the course of treatment, the loss of 48 lb., coinciding with a very marked natriuresis during chlorothiazide administration at 2 gm./day for three weeks, the cessation of proteinuria following dexamethasone administration at 4 mg./day for 10 days, the progressive rise in serum complement, the decrease in blood urea and serum cholesterol, and the progressive rise in serum albumin. This total remission in proteinuria and edema has now persisted for two years.

in total urinary 17-hydroxycorticosteroid accompanied by a marked decrease in the conjugated fraction. The remission of proteinuria was short, since it recurred a month later at the same previous levels (FIGURE 3).

Important natriuresis induced by the simultaneous administration of spironolactone and chlorthalidone is illustrated in a 52-year-old man with nephrotic syndrome secondary to diffuse membranous glomerulonephritis (FIGURE 4). This patient was admitted to the hospital with marked pitting edema over

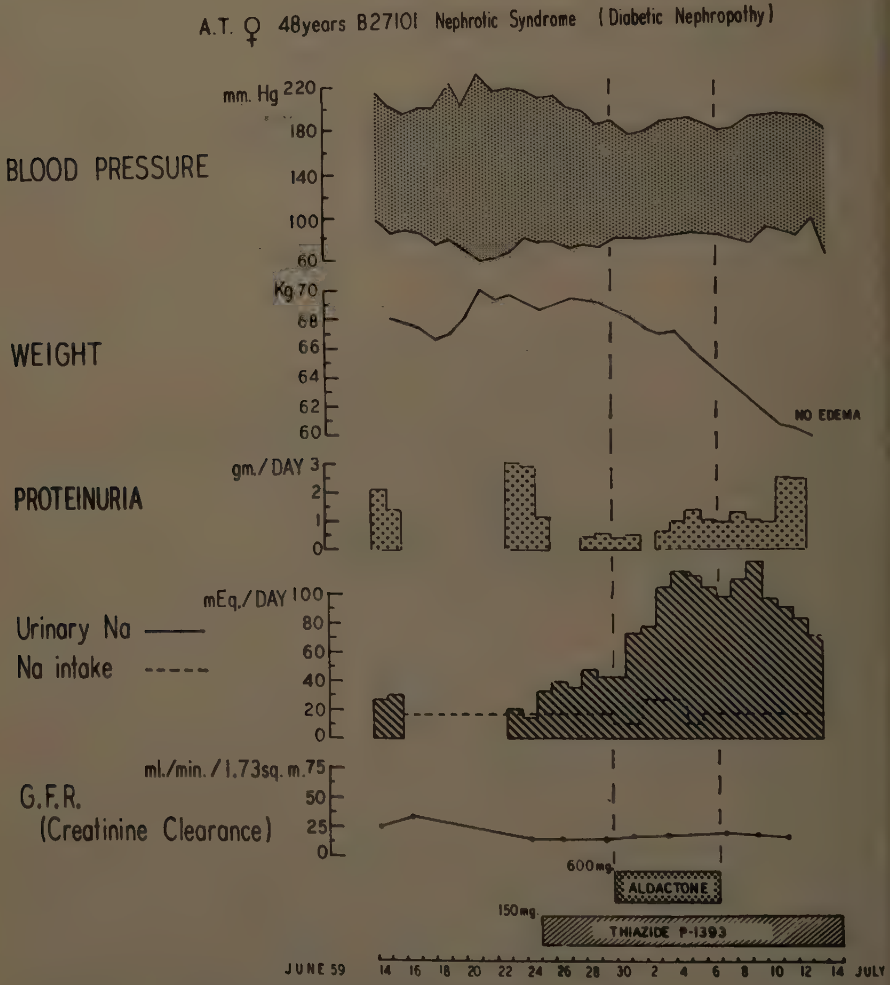

FIGURE 2. Patient A.T. During administration of a thiazide derivative, P-1393, there was a slight fall in recumbent systolic pressure and a slightly negative sodium balance. The addition of spironolactone at 600 mg./day for seven days produced a marked loss of weight and edema and enhanced markedly the natriuresis, which persisted for eight days following cessation of spironolactone. Complete disappearance of edema with a weight loss of 10 kg. was obtained despite a glomerular filtration rate, approximately measured by the creatinine clearance, of about 20 ml./min./1.73 sq. m. of surface area.

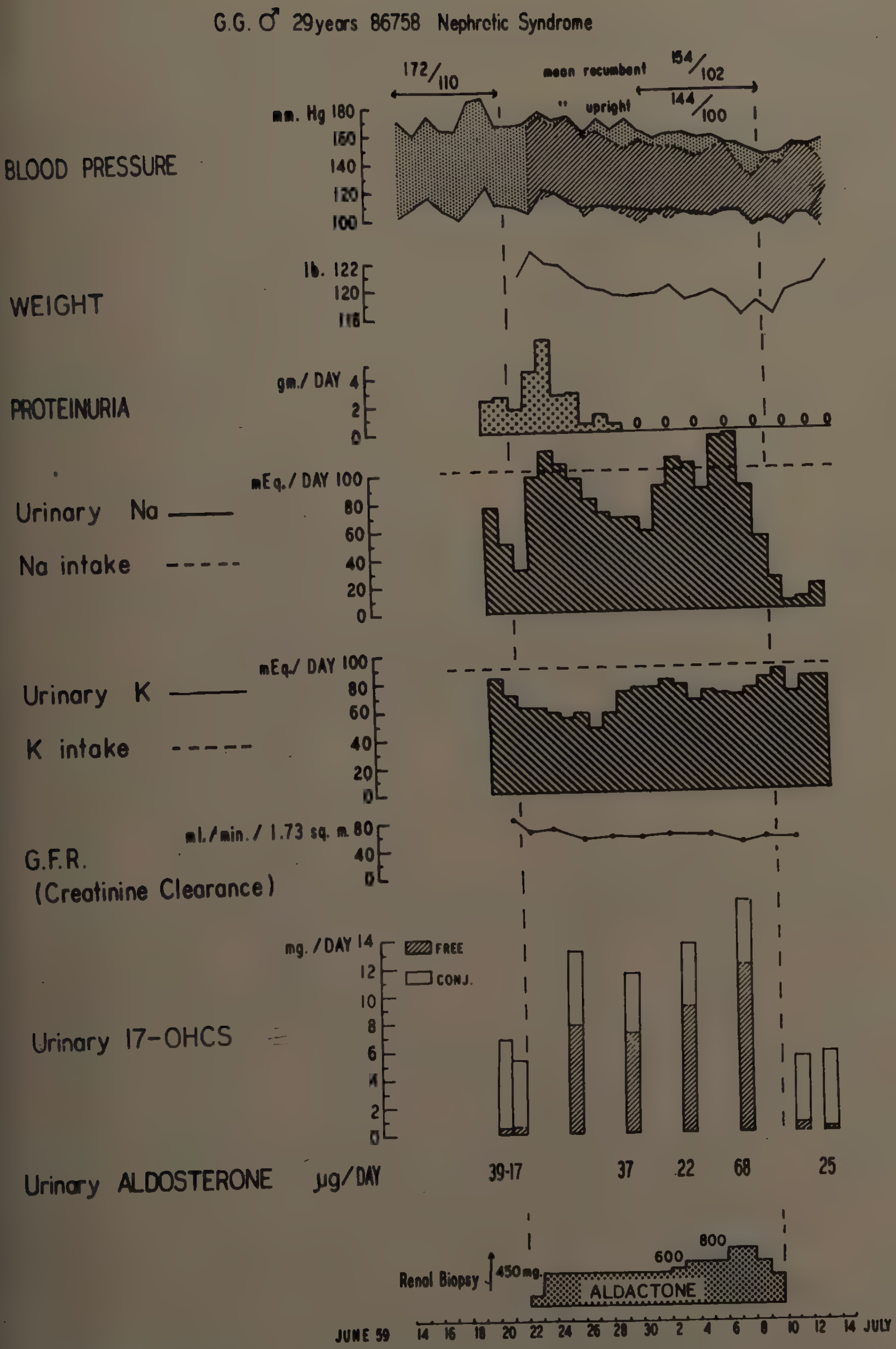

FIGURE 3. Patient G.G. Administration of spironolactone at a dosage of 450 to 800 mg./day for 17 days resulted in a progressive decrease in blood pressure, a loss of 4 lb., complete cessation of proteinuria, and no significant change in sodium balance except for the very marked sodium retention following cessation of spironolactone. The total urinary 17-hydroxycorticosteroids rose during administration of spironolactone, with a concomitant marked decrease in the conjugated fraction. Urinary aldosterone rose during the latter part of spironolactone administration when dosage was at 800 mg./day.

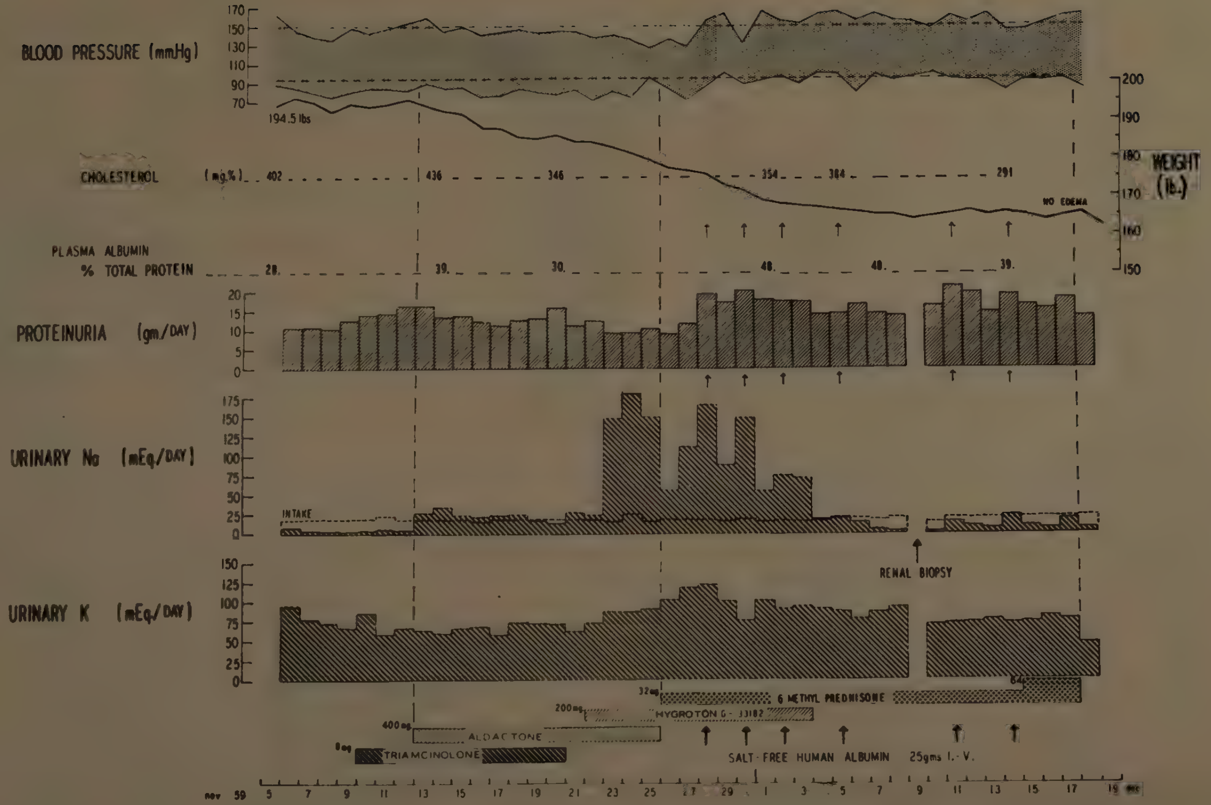

FIGURE 4. Patient H.M. Administration of triamcinolone and of 6-methyl prednisolone brought no change in proteinuria. Spironolactone given at 400 mg./day for 9 days produced a progressive loss of weight with a slight negative sodium balance. Addition of chlorthalidone at 200 mg./day for 4 days brought a very marked natriuresis with further fall in weight. This natriuresis continued to moderate degree with administration of this isoindoline derivative for another 8 days. The patient lost 33 lb. and left the hospital completely free of edema. Administration of 6-methyl prednisone produced a slight but consistent rise in systolic and diastolic pressures (the daily B.P. indicated is the average of 14 hourly readings from 8 A.M. to 10 P.M.).

both legs, genitalia, and lumbosacral region. Administration of triamcinolone for 10 days and of 6-methyl prednisolone for 24 days did not bring any decrease in proteinuria. A marked natriuresis with complete loss of edema was observed during the period of simultaneous administration of spironolactone and chlorthalidone. Natriuresis was less marked during administration of either drug alone.

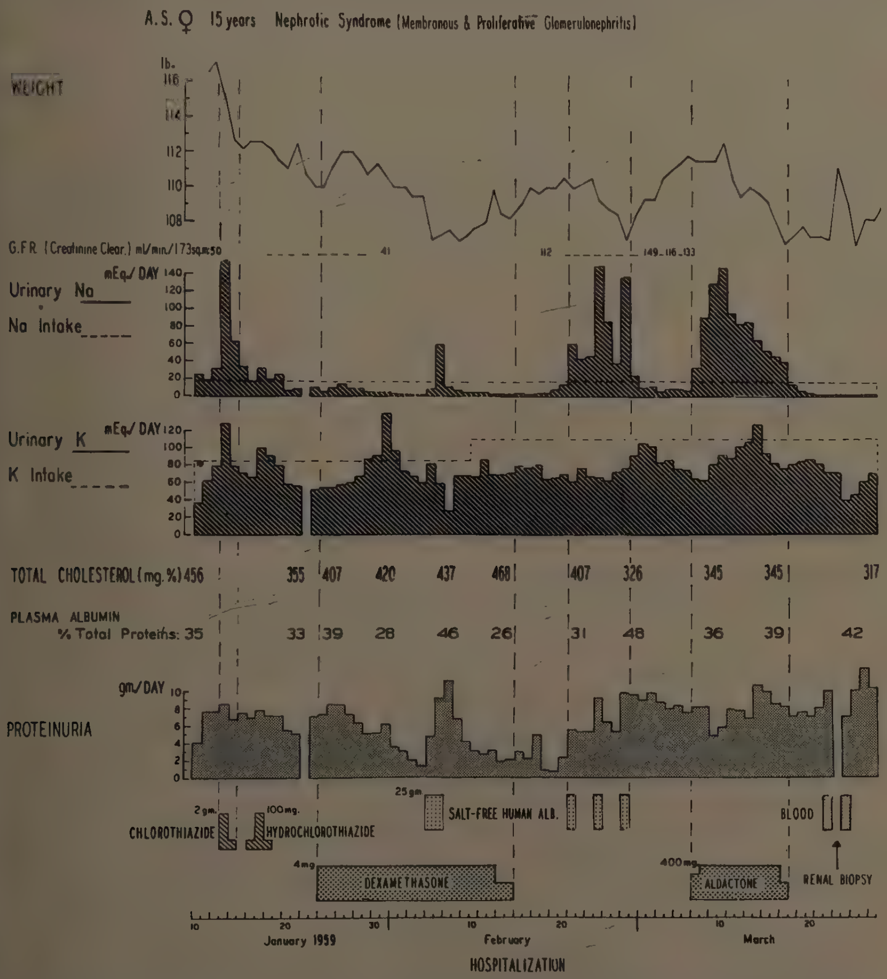

FIGURE 5. Patient A.S. The diuretic effects of chlorothiazide, hydrochlorothiazide dexamethasone, salt-poor concentrated human albumin, and spironolactone are compared The most intense natriuretic periods are those during administration of chlorothiazide, infusions of 25 gm. of concentrated salt-poor human albumin, and administration of spironolactone. The latter period is shown in greater detail in FIGURE 6.

The diuretic effects of chlorothiazide, salt-poor concentrated human albumin, and spironolactone in a 15-year-old girl with nephrotic syndrome due to mixed glomerulonephritis, can be seen in FIGURE 5. Administration of 2 gm. of chlorothiazide for one day resulted in a marked natriuresis, which was repeated to the same degree on two different days during which the patient received infusions of 25 gm. of salt-poor concentrated human albumin. However, the most marked and prolonged natriuresis was obtained with spironolactone, the study of which is shown in greater detail in FIGURE 6. Administration of this

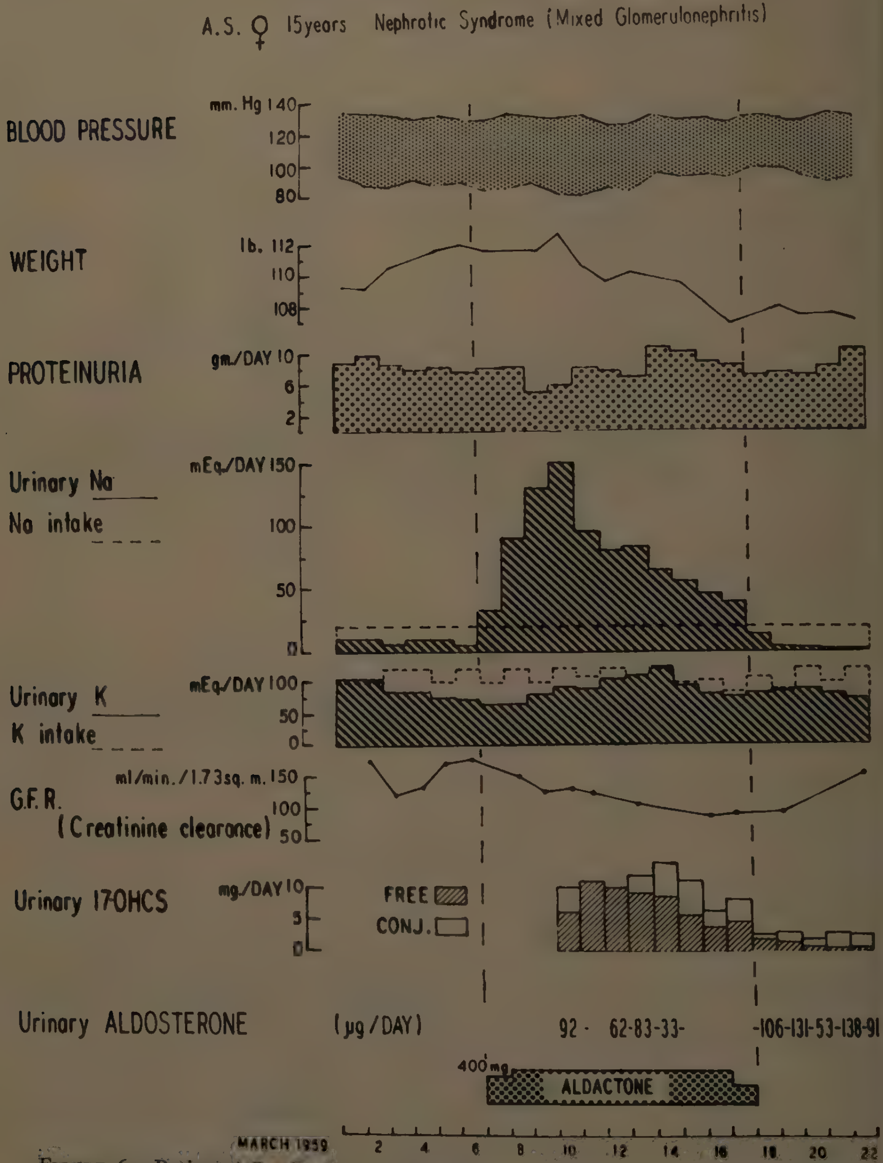

FIGURE 6. Patient A.S. During spironolactone administration at 400 mg./day for 11 days, there was a progressive loss of weight of 5 lb., no change in proteinuria, a markedly increased natriuresis, a slight fall in creatinine clearance, and an increase in urinary total 17-hydroxycorticosteroids, accompanied by a very marked fall, to the stage of complete disappearance of the conjugated fraction. Urinary aldosterone is at high levels during and after spironolactone administration.

agent at a dosage of 400 mg./day for 11 days was accompanied by a loss of 5 lb., a very marked and continued natriuresis for the whole period of administration, and no change in proteinuria. Again, there is a significant increase in total urinary 17-hydroxycorticosteroids, with a marked decrease and even a disappearance of the conjugated fraction. Urinary aldosterone is at very high levels both during and following administration of spironolactone. Unfortunately, urine collections made during the control period previous to the administration of the drug were lost. Two renal biopsies were done in this patient. The first one, in 1957, when the patient was admitted with generalized edema following a severe cold and fever, showed changes of acute glomerular nephritis with mixed proliferative and membranous lesions. At the time of the metabolic balance study in March 1959, the second renal biopsy showed changes chiefly of membranous and of proliferative glomerulonephritis.

The case of a sixth patient, a 26-year-old man with nephrotic syndrome due to membranous glomerulonephritis, is shown in FIGURE 7. Administration of dexamethasone and of 6-methyl prednisolone brought a very slight negative sodium balance with a progressive loss in weight and disappearance of edema. A somewhat more marked natriuresis was produced by spironolactone and shown in greater detail in FIGURE 8. As may be seen, during spironolactone administration at 450 to 600 mg./day for two weeks, there was a significant negative sodium balance and a slight decrease in glomerular filtration rate, as measured approximately by creatinine clearance. No change in proteinuria occurred. The conjugated fraction of the 17-hydroxycorticosteroids was again decreased during administration of spironolactone, and urinary aldosterone was generally increased during period of administration of the drug.

The last case we discuss is that of a 62-year-old woman with the nephrotic syndrome secondary to diabetic nephropathy and in the terminal stage (FIGURE 9). At the time of admission, the patient was in marked anasarca with severe orthopnea, cyanosis, profuse sweating, and mild hypertension. There was a right pleural effusion with moist rales over both lung bases. Creatinine clearance was 15 to 20 ml./min./1.73 sq. m. of surface area. Blood urea was 65 mg. per cent. The patient received as basic therapy spironolactone at 500 mg./day for 54 days and, in addition, on various occasions, other natriuretics, such as chlorothiazide, hydrochlorothiazide, flumethiazide, and meralluride. The most important natriuretic periods were those during which the patient received simultaneously spironolactone, a thiazide compound, and/or meralluride. Association of flumethiazide and meralluride was also equally effective. This patient, despite the very low glomerular filtration rate that remained constant throughout her course in the hospital, was able to leave the hospital with only a slight amount of pleural effusion.

The Management of Some Aspects of Nephrotic Syndrome

The nephrotic syndrome is indicated chiefly by percutaneous renal biopsy. When the etiological diagnosis is firmly established, the treatment of the nephrotic syndrome must be oriented primarily toward cessation of the massive proteinuria and correction of its secondary biochemical and physiological effects (TABLE 3). Cessation of proteinuria may occur "spontaneously" during bed rest and administration of a diet rich in protein (1.7 to 2 gm./day/kg. of

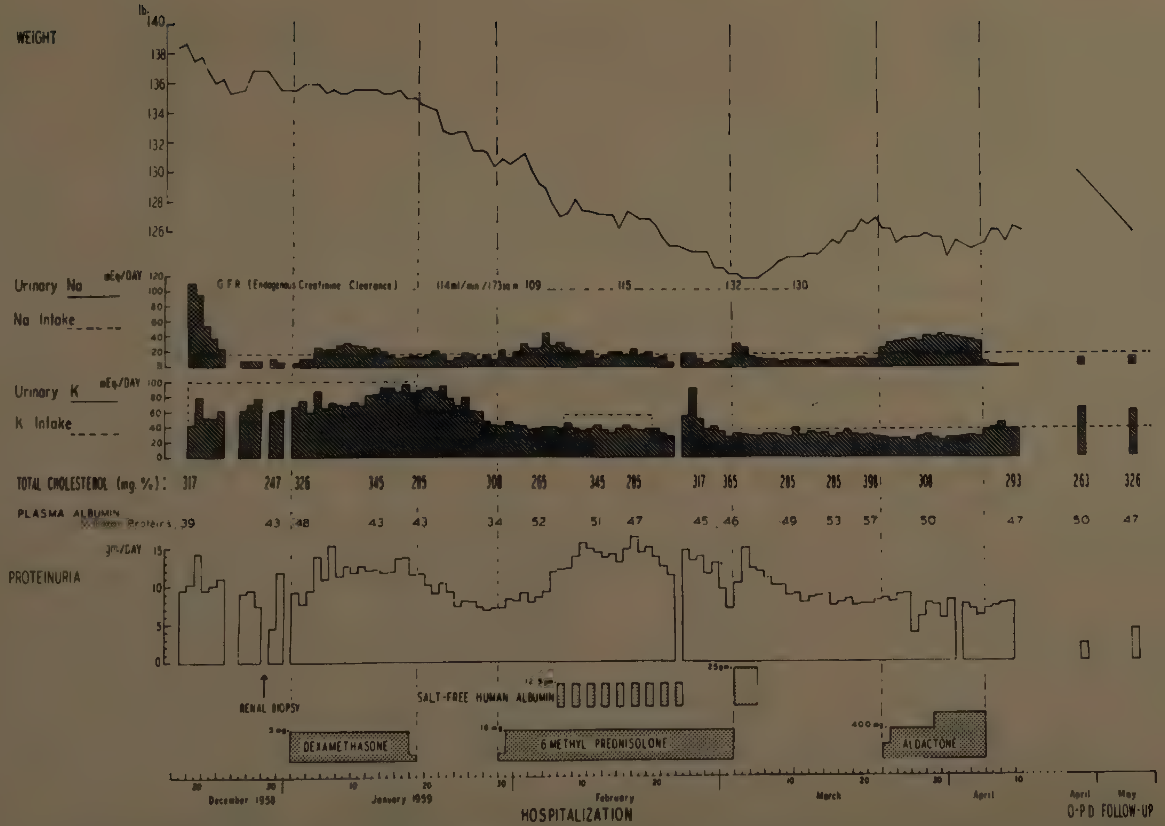

FIGURE 7. Patient D.L. The effects of dexamethasone, 6-methyl prednisolone, and spironolactone are compared in a 26-year-old patient with nephrotic syndrome secondary to membranous glomerulonephritis. Bed rest was responsible in the early part of this study for the initial marked natriuresis. Despite a progressive loss in weight of 15 lb. no significant change in proteinuria was observed during the administration of the three steroids. A slight and consistent negative sodium balance was obtained only during spironolactone. This is illustrated in greater detail in FIGURE 8.

body weight) and low in sodium (below 500 mg./day). The occurrence of such a complete remission in a patient with a so-called cyclic nephrotic edema[4] is illustrated in FIGURE 10. It constitutes a very rare exception. In most other cases (especially those due to intrinsic renal diseases and disseminated lupus erythematosus), administration of corticosteroids, such as prednisolone, 6-

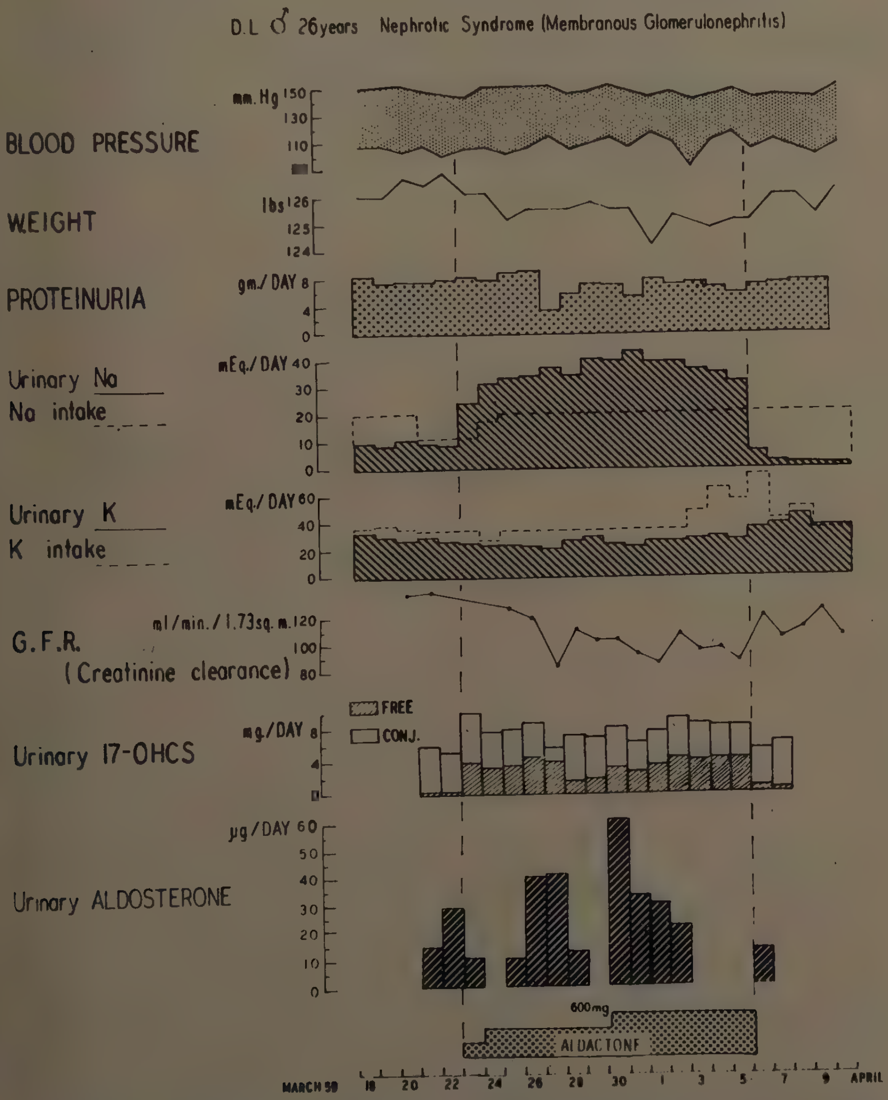

FIGURE 8. Patient D.L. Administration of spironolactone at 400 to 600 mg./day for two weeks produced a slight natriuresis with a fall in glomerular filtration rate, approximately measured by creatinine clearance, and an increase in urinary total 17-hydroxycorticosteroids with a significant decrease in the conjugated fraction. Urinary aldosterone generally increased during the administration of spironolactone.

methyl prednisolone, triamcinolone, or dexamethasone, in high dosage for periods of 15 to 30 days, has now become the treatment of choice in hospitals, and will bring, in a certain number of patients, chiefly children, a cessation of proteinuria with disappearance of edema and correction of blood biochemical abnormalities. The mode of action of corticosteroids in producing either diuresis or cessation of proteinuria is, after 10 years of empirical use, as obscure as when they were first used in 1950.[7,14,23]

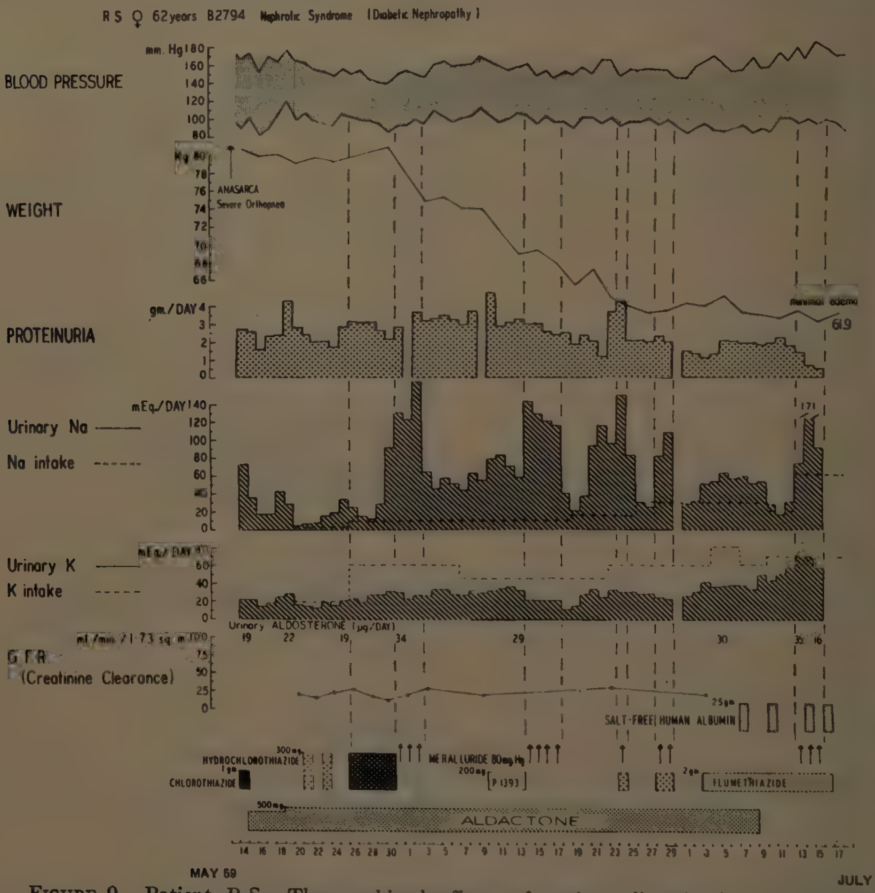

FIGURE 9. Patient R.S. The combined effects of various diuretic drugs, including spironolactone, thiazide derivatives, and/or meralluride, which produce striking effects with almost complete relief of edema in a patient with severe diabetic nephropathy and with a very low glomerular filtration rate of 15 to 20 ml./min./1.73 sq. m. of surface area. Association of spironolactone with a thiazide compound and/or meralluride produces very marked natriuresis. Similar natriuresis was obtained by the combined administration of flumethiazide with meralluride. Urinary aldosterone is increased (normal excretion: 1.5 to 9.5 μg./day) and does not show any significant change before, during, or after periods of natriuresis.

Relapses and recurrences are fairly frequent following steroid therapy and patients should be retreated in the same way, perhaps at higher dosages and for a more prolonged period of time.[9] This treatment is generally not as suc-

TABLE 3
NEPHROTIC EDEMA

Factors involved	Therapeutic measures
Proteinuria (mechanism unknown) Decrease in plasma osmotic pressure Hypoproteinemia Hypoalbuminemia Hypercholesterolemia Hyperlipemia Interstitial edema Decreased blood volume Stimulation of aldosterone Increased tubular reabsorption of sodium	Corticosteroids (mode of action unknown) Dietary measures High protein intake (1.7–2.0 gm./kg./day) Low sodium (400 mg./day) I.V. concentrated human albumin Diuretic agents Spironolactone Thiazide derivatives Sulfamyl isoindoline derivatives Organic mercurials Steroids

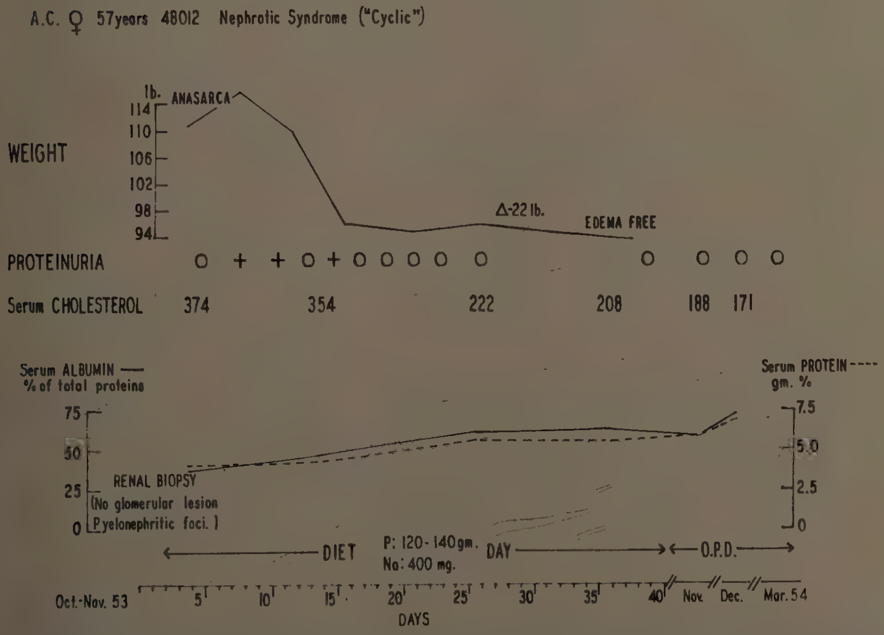

FIGURE 10. This patient has a clinical history of four distinct episodes of nephrotic syndrome separated by intervals of complete remission of proteinuria and edema. One such episode was observed in the medical ward prior to the organization of the Hôtel-Dieu de Montréal's Metabolic Unit. Marked loss of weight (22 lb.) with complete remission of edema and of proteinuria followed bed rest and administration of a high protein, low sodium diet. This was accompanied by a progressive fall in serum cholesterol, a parallel rise in total serum protein, and a rise in serum albumin fraction. This patient was studied later during a nephrotic episode in 1958 and complete remission of proteinuria and edema was obtained during administration of hydrocortisone. Renal biopsy done at that time failed to show any glomerular lesion with the light microscope, but presented evidence of pyelonephritis.

cessful in adults with the nephrotic syndrome as it is in children. Because of this fact and the high relapse rate, some workers have recently advocated the long-term intensive use of corticosteroids in adults, and have claimed much better results in small series of patients.

This is not without severe dangers, as strongly emphasized in 1957 by Good and his co-workers,[8] who reported side reactions of "sufficient severity to threaten life" in 10 per cent of a series of 340 children treated with ACTH or cortisone for long periods of time. These severe complications, listed in part in TABLE 4, did not include the many other annoying side effects occurring in almost all patients on long-term therapy.

Without any better knowledge of the mode of action of corticosteroids and of the basic factors responsible for massive edema and proteinuria, we wonder if such enthusiasm for long-term intensive corticosteroid treatment for all patients with nephrotic syndrome is warranted at the present time, and if the beneficial effects of corticosteroids in some cases outweigh the severe life-threatening reactions in others and the annoying side-effects in almost all patients. The efficacy of the new natriuretic agents makes the use of this procedure, at least for diuretic purposes, doubtful if not unwise. We feel that, except for the indications given by Morrison[15a,b] in cases of resistant edema associated with hyponatremia, there is little need now for the long-term intensive use of corticosteroids for diuretic purposes in the management of patients with nephrotic syndrome. The discovery of the new natriuretic agents, such as spironolactone, chlorothiazide and its derivatives, and chlorthalidone has greatly facilitated the treatment of nephrotic syndrome in permitting complete relief of edema in almost all cases. Their use in association is particularly valuable in patients with a very low glomerular filtration rate. Our results confirm in general those obtained by Schreiner.[22c]

TABLE 4
LONG-TERM INTENSIVE CORTICOSTEROID ADMINISTRATION FOR TREATMENT OF NEPHROTIC SYNDROME

"Necessary" adjuncts	Severe reactions	Side effects
Na restricted diet	Hypertensive encephalopathia	Hypertension
Supplementary K	Status epilepticus	Hypokalemic alkalosis
Frequent feedings	Gastrointestinal	Peptic ulcer (?)
Antacids	Hemorrhage	
Antibiotics	Perforation	Tendency to infections
	Septicemia	Acne
	Severe osteoporosis with fractures	Moon-face
		Hirsutism
		Behavior changes
		Diabetes

These new diuretics should preferably be used in conjunction with a diet restricted below 500 mg. of sodium per day and containing 1.7 to 2.0 gm. of proteins per kg. of body weight per day. Bed rest should be enforced for all patients with various degrees of edema. When chlorothiazide or one of its derivatives, or chlorthalidone is used, supplementary potassium should always be administered in the form of fruit juices (700 to 1000 ml./day) or of potassium chloride (2 to 4 gm./day) because of the increased kaliuresis. Spironolactone has no such potassium-depleting effect but, if administered for prolonged periods, can produce severe hyponatremia.

Plasma determinations of chloride, sodium, and potassium should be done at frequent intervals for prevention of salt-depletion syndrome, of hypochloremic alkalosis, and of hypokalemia, with subsequent danger of digitalis intoxication.

Conclusions

Our studies of 13 patients with nephrotic syndrome of various origins indicate that the new natriuretic agents, spironolactone, chlorothiazide and its derivatives, and chlorthalidone are effective in relieving edema due to nephrotic syndrome. Administration of spironolactone in the patients studied is accompanied by a rise in total urinary 17-hydroxycorticosteroids, probably due to a metabolite excreted in urine and reacting with the Silber-Porter reagent.[20] This rise is accompanied by a marked decrease and even a disappearance of the conjugated fraction. Spironolactone is also accompanied in most cases by a significantly increased aldosteronuria. Association of spironolactone with organic mercurials and/or chlorothiazide (or one of its derivatives) or chlorthalidone produces a marked enhancement of natriuresis. We feel that the association of these new diuretics constitutes a very effective and most rational approach to the treatment of nephrotic edema.

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COMBINED DIURETIC AND STEROID THERAPY IN CIRRHOSIS WITH ASCITES*

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The patient with cirrhosis of the liver and ascites is severely hampered by immobilization, loss of appetite, dyspnea from elevation of the diaphragms or escape of fluid into the pleural space, and the development of umbilical and inguinal hernias. Although strict maintenance of "dry weight" is probably not indicated until liver function has spontaneously improved, a reduction in the amount of retained fluid is desirable when ascites is marked. Most patients become resistant to single diuretic agents before any significant portion of the extra fluid has been removed, and continued administration of the usual agents results in severe potassium depletion. A generous paracentesis has the disadvantages of further loss of protein in patients who are already protein-depleted, occasional hepatic coma, not-infrequent vascular collapse, and severe dilutional hyponatremia if the patient's fluid intake is not restricted.

Availability of an effective aldosterone antagonist has led to the observation that combinations of diuretics with different modes of action may facilitate successful diuresis of previously resistant patients.[1-5] In this study the mean change in excretion of sodium, potassium, and water, averaged over a three-day period, has been determined for four single different diuretic agents and various combinations of the four. The results suggest that a combined approach offers, for the first time, a method of diuresing patients with previously intractable ascites.

Materials and Methods

Thirty-six patients with cirrhosis of the liver and resistant ascites were studied in a metabolic ward. No patient with a urine volume of less than 500 ml./day was admitted to the study. The diet contained 10 mEq. or less of sodium and 80 ± 10 mEq. of potassium. In addition, the patients received 10 mEq. of potassium chloride in tomato juice four times a day. Fluid intake was set at a constant level determined by taking a mean of three days of an ad-lib intake. Body weight was obtained daily at the beginning of each 24-hour collection period. The urinary concentration of sodium, potassium, and creatinine was determined daily. Accuracy of collection was assessed by the constancy of the 24-hour creatinine excretion. Blood was drawn at the beginning of administration of the agents and again three days later, and hematocrit, NPN, creatinine, sodium, potassium, and carbon dioxide combining-power levels were obtained.

The agents evaluated were a glucocorticoid—prednisone (10 mg.) or methylprednisolone (8 mg.)—every 8 hours; spironolactone, 100 mg. every 8 hours; chlorothiazide, 1 gm. every 12 hours; and meralluride (Mercuhydrin) 2 cc.

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I.M., once daily. The mean daily excretion of sodium, potassium, and water was determined for the three days prior to treatment and the first three days of treatment. The difference between these two was assumed to be caused by the diuretic agents. The mean daily weight change during the three days of treatment was calculated from the weight at the start and end of treatment.

In FIGURES 1, 2, 3, and 4, each point represents the mean change for one patient. The heavy line is the mean of the group, and two standard errors in each direction are indicated by the enclosed box. If the box enclosing the mean ± 2 S.E. does not encompass the zero line, the change is probably significant. If the boxes of two groups do not overlap, the difference in means is probably statistically significant.

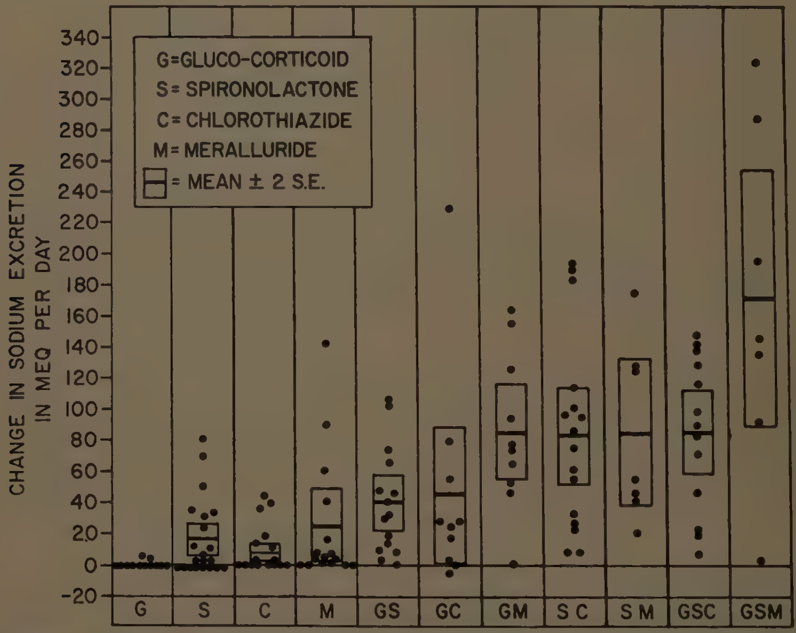

FIGURE 1. Effects of various agents on urinary sodium excretion in patients with cirrhosis of the liver. Each point represents the mean daily change in each patient during a 3-day treatment period compared to a base-line period.

Results

FIGURE 1 summarizes the changes in the mean daily sodium excretion in the first three days of consecutive administration of the various agents used alone and in combination. The glucocorticoids induced no increase in sodium excretion. Spironolactone increased the sodium excretion on the average, but a large group showed no response. Similarly, chlorothiazide or meralluride used alone caused little natriuresis in most patients, although a few responded. However when a glucocorticoid was added to chlorothiazide, spironolactone, or meralluride there was a marked reduction in the number of patients who showed

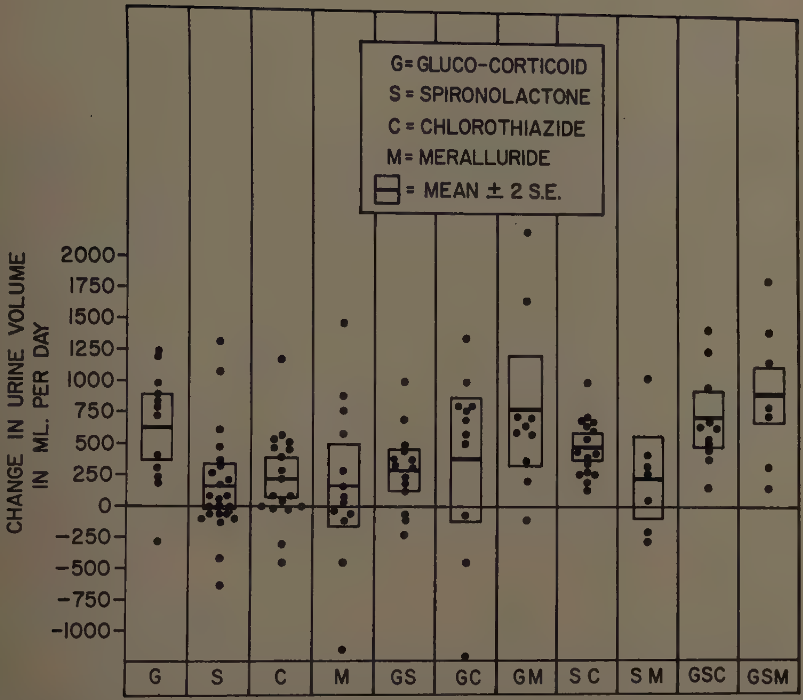

FIGURE 2. Effects of various agents on urine volume in patients with cirrhosis of the liver. Each point represents the mean daily change in each patient during a 3-day treatment period compared to a base-line period.

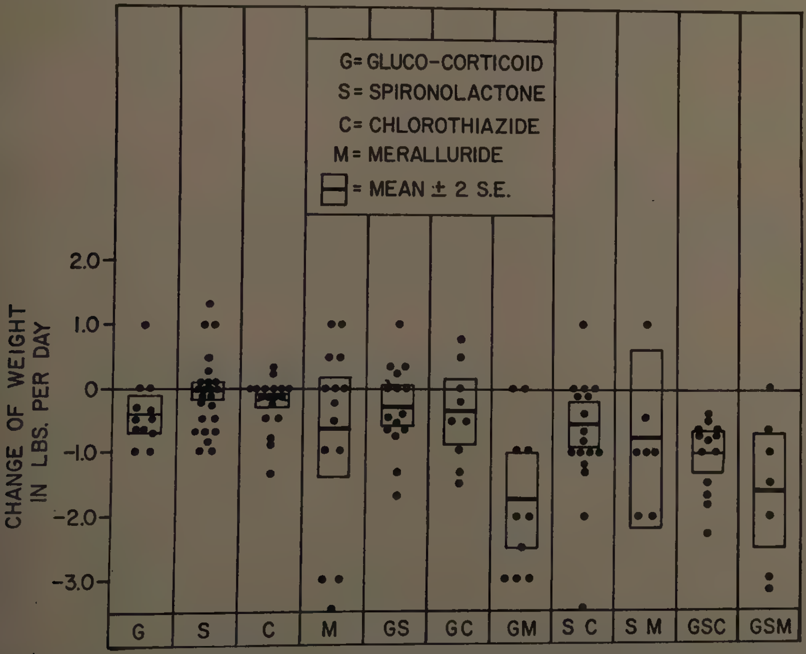

FIGURE 3. Effects of various agents on body weight in patients with cirrhosis of the liver. Each point represents the mean daily change in each patient during a 3-day treatment period compared to a base-line period.

no response, and the mean sodium excretion for the group rose to clinically significant levels, between 40 and 80 mEq./day. Also, when spironolactone was added to chlorothiazide or meralluride a marked potentiation of sodium excretion was noted. When a glucocorticoid and spironolactone were both added either to chlorothiazide or meralluride, a marked natriuresis was noted. The greatest mean daily excretion of sodium was noted with a glucocorticoid, spironolactone, and meralluride.

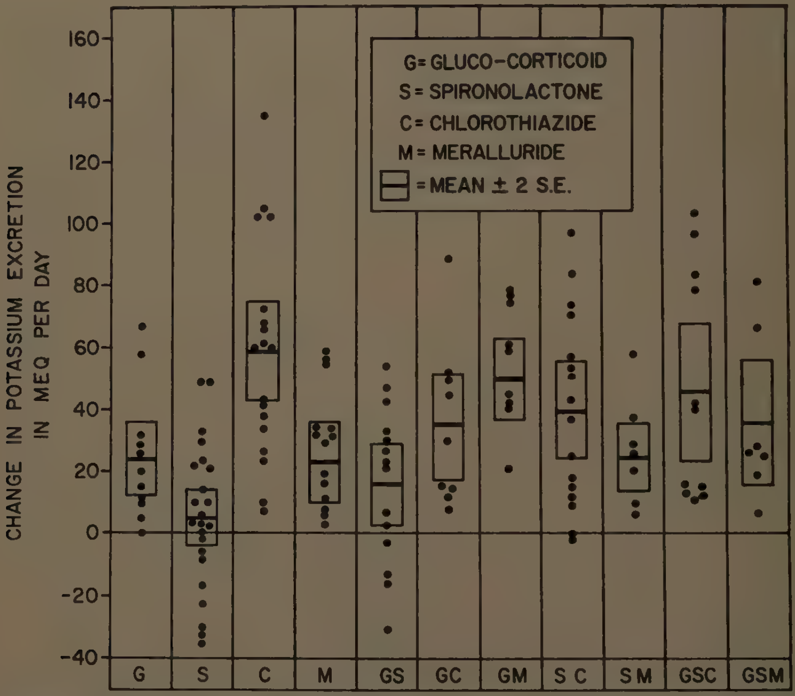

FIGURE 4. Effects of various agents on urinary potassium excretion in patients with cirrhosis of the liver. Each point represents a 3-day treatment period compared to a base-line period.

FIGURE 2 shows the changes in urine volume. Prednisone and methylprednisolone induced a definite increase in water excretion in most patients. This was a larger increase than that caused by spironolactone, chlorothiazide, or meralluride alone. When a glucocorticoid or spironolactone was added to the other three agents there was usually a potentiation of water excretion. When a glucocorticoid was added to the combination of spironolactone with chlorothiazide or meralluride the water excretion was again increased. The changes in weight presented in FIGURE 3 reflected the changes in urine volume.

Three of the four agents caused a significant potassium loss, most marked with chlorothiazide (FIGURE 4). When administered alone, spironolactone did not significantly affect potassium excretion. On all of the various combinations used in this study there was a significantly elevated potassium excretion over the base line values, and spironolactone had only a slight protective effect when combined with other agents. None of these agents used alone or in combination resulted in any significant change in the endogenous creatinine clearance.

There were no significant changes in carbon dioxide combining power, serum chloride, and nonprotein nitrogen. Data on the 3-day changes in sodium and potassium are presented in FIGURES 5 and 6. Sodium concentration rose significantly with glucocorticoid alone and in combination with spironolactone, and fell when glucocorticoid, spironolactone and chlorothiazide were given together. When spironolactone was given alone the serum potassium level rose by 0.34 ± 0.17 mEq./l. (mean ± 1 S.E., not quite significant), and it fell significantly on chlorothiazide and the combination of glucocorticoid and meralluride.

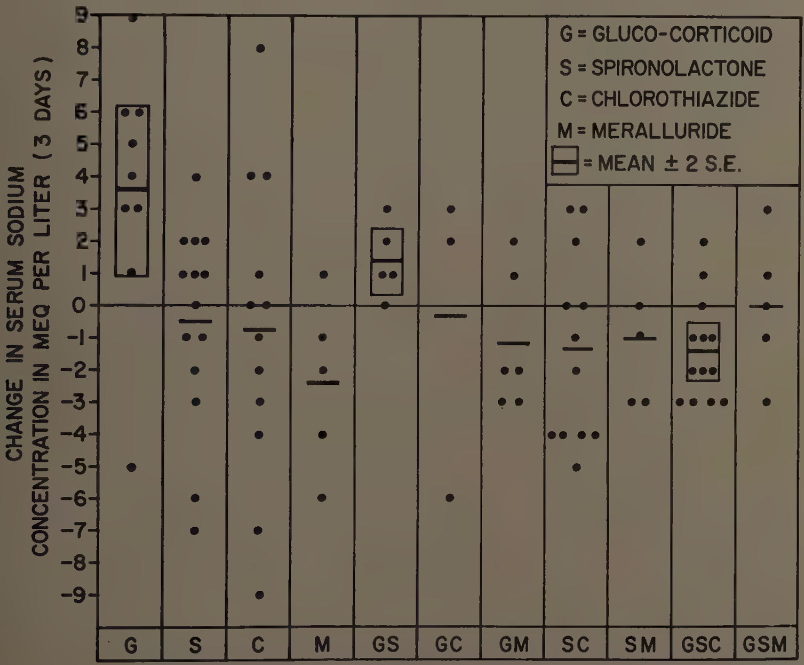

FIGURE 5. Effects of various agents on serum sodium concentration in patients with cirrhosis of the liver. Each point represents the change in each patient during a 3-day treatment period.

Discussion

Discussion of these data should be preceded by certain comments on the difficulties inherent in the evaluation of diuretic agents in man. Patients with fluid retention complicating cirrhosis vary greatly from day to day in their response to the same diuretic agent. A single day's observation is not a valid assessment of the relative effects of different agents, and increasing resistance complicates studies lasting longer than a few days.[6] For these reasons a 3-day period was chosen. It is important to emphasize that differences in relative effectiveness may depend on whether or not the data are gathered during the period of maximum activity. For instance, chlorothiazide and the mercurials have a maximum effect in the first two days of continuous administration, while the peak effect of spironolactone and the glucocorticoids may not appear for two or more days. The effects of administering these agents for longer periods of time are currently being investigated.

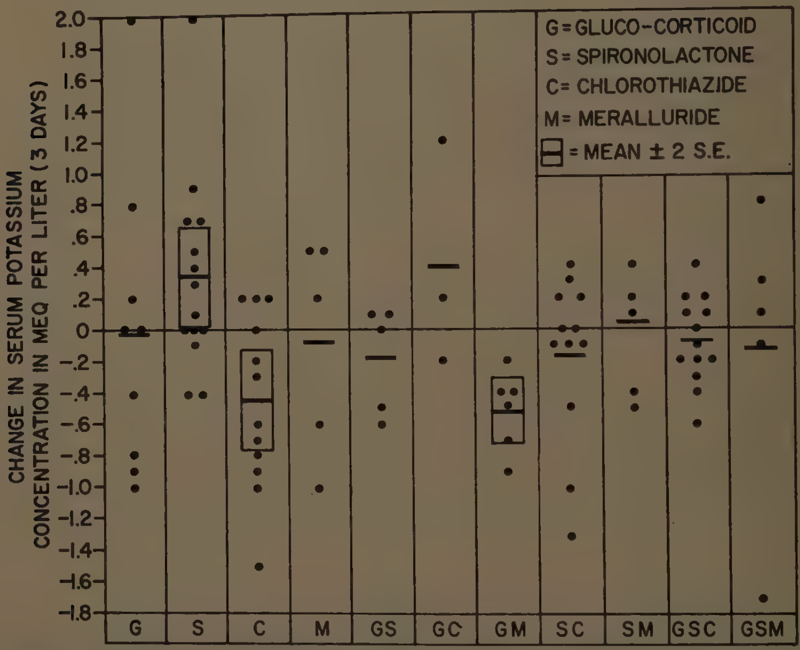

FIGURE 6. Effects of various agents on the serum potassium concentration in patients with cirrhosis of the liver. Each point represents the change in each patient during a 3-day treatment period.

The data presented above would be more meaningful if all drugs were given in all combinations to all patients in a random manner, preceded by a suitable control period. This was not possible because of the different rates at which patients lost their fluid, and because there were occasionally marked changes in the capacity of an individual patient to diurese. Most of the patients received multiple combinations of the drugs.

Furthermore, the 36 patients included in this study represent a highly select population of cirrhotics. They had been transferred to the Lemuel Shattuck Hospital from other hospitals in the area because they failed to respond to the usual diuretic measures, and they were then moved to the metabolic ward for study only if they failed to respond significantly to a low-sodium diet plus mercurials or chlorothiazide. Although urinary levels of aldosterone were not determined, it is probable that all the patients had severe secondary hyperaldosteronism.

The data offer some basis for speculation on the mode of action of these different diuretic agents. The glucocorticoids, prednisone and methylprednisolone, significantly increase water and potassium excretion when given alone and potentiate sodium excretion without further increasing potassium loss when given with the other agents. The effects on water excretion in patients with cirrhosis have been pointed out before[7-10] but have not been adequately explained. The increase in potassium excretion may be a manifestation of the "mineral-corticoid" or antianabolic effects of these agents. Potentiation of sodium diuresis when the glucocorticoids are given in conjunction with the more natruretic agents may be an indirect result of an increased glomerular filtration rate or decreased reabsorption of water in the proximal tubules. However, endogenous creatinine clearances in these patients do not support the theory that increased glomerular filtration rate accompanies glucocorticoid administration. A "feedback" decrease in aldosterone excretion with glucocorticoid administration has been suggested[11] but not confirmed.[8]

The differences in the ratio of sodium to potassium excretion when spironolactone, chlorothiazide, or meralluride is given alone suggest a distinctly different mode of action for each. The first has a mild natruretic effect with no net change in potassium excretion; the second has a marked kaluretic action; and the third lies between spironolactone and chlorothiazide in its effects.

It has been suggested that spironolactone protects patients against the excessive kaluretic effects of chlorothiazide,[12] but this is not apparent from the data reported above. Except for spironolactone administered alone, all drugs and combinations result in a distinctly negative potassium balance. It is possible that with long-term therapy potassium loss per day may be less, but unpublished data from this laboratory indicate that most patients are still in negative potassium balance even when a high intake of potassium is maintained by supplements.

These observations on the relative effects of the four agents alone and in combination have distinct practical implications. From the theoretical standpoint the combination of three agents, a glucocorticoid to effect water excretion, chlorothiazide or its derivatives or a mercurial to effect sodium reabsorption in the proximal tubule, and spironolactone to diminish sodium reabsorption in the distal tubule, should be most effective in diuresing the refractory patient. The advantage of three agents over two is not apparent in these 3-day studies, but longer courses of treatment have revealed a greater effect of the triple combination.[13] For potentiation of sodium excretion, spironolactone is the drug of choice because of its minimal toxicity. In patients with dilutional hyponatremia the glucocorticoids are probably indicated.

Summary

(1) Patients resistant to single diuretic agents—glucocorticoids, chlorothiazide, spironolactone, and meralluride—usually respond to any combination of two or more drugs having different modes of action.

(2) When used alone the major effect of the glucocorticoids was on water excretion; chlorothiazide had its largest effect on potassium excretion.

(3) Combinations of two or more drugs resulted in significant losses of sodium, potassium, and water. The predominant effect of spironolactone was on sodium excretion while the glucocorticoids induced greater water excretion.

Acknowledgments

We thank Ann Long and Margaret Wilcox for supervising the study of patients in the Metabolic Unit, Sheila Dye for supervising the diets, and Martha Boardman for carrying out the laboratory analyses.

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THE USE OF THE NEWER DIURETICS IN THE TREATMENT OF CARDIAC DISEASE

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The introduction of chlorothiazide in 1957 was rapidly followed by that of several analogues of the benzothiadiazine series. Slight changes in basic structure have been noted to alter markedly the potency of the drug, while less marked but definite changes occur in the electrolyte excretion pattern. One of the most significant of these changes has been the reduction in potassium excretion with the trifluoromethyl derivatives. Hydrochlorothiazide, flumethiazide, hydroflumethiazide, and benzydroflumethiazide, in addition to benzothiadiazine, are all potent oral diuretics, approaching the parenteral mercurial diuretics in effectiveness. While they are not as potent in single-dose administration as mercurials, they are superior to the mercurials for diuretic practice in many ways. The practical and economic advantages of oral therapy are obvious. The drugs have been extremely well tolerated, have a low incidence of toxicity, remain effective on repetitive or continuous administration, produce increased sodium excretion and water loss, and tend to stabilize a patient who is accumulating edema fluid more readily than might the sporadic intermittent mercurial program. More recent derivatives are currently being evaluated in our clinical practice.

All of these agents inhibit primarily the renal tubular reabsorption of sodium and chloride, with water loss occurring secondarily: an action similar to that of the mercurials. Increased potassium excretion caused by these agents has important clinical implications. Diuresis is initiated approximately 2 hours after an effective oral dose, and continues for 6 to 12 hours thereafter.

These important advances in the field of diuretic therapy have not supplanted the basic indications in the treatment of congestive heart failure, which continue to be digitalis, rest, and a reasonable reduction in the dietary intake of sodium. These first measures suffice in many instances of early cardiac decompensation. It also follows that when diuretics become necessary the choice of drug and dosage must be tailored to the needs of the individual patient. The use of the minimal effective dose will lessen the likelihood of undesired effects and, possibly, toxicity. A schedule of diuretic administration on one or two days of each week may keep a patient free of edema, while more advanced cases may necessitate a daily diuretic regimen.

An additive effect may be observed by the concomitant use of one of these agents plus a mercurial diuretic. This has been useful in some cases of resistant congestive failure and in patients approaching the refractory phase of their disease. A few instances of gratifying results in these advanced cases have also been seen when a benzothiadiazine has been combined with adrenocortical steroids or the spirolactones.

The effective dose of chlorothiazide or flumethiazide is 1 to 2 gm. daily in two divided doses. This results in a significantly greater diuresis than that produced by a large single dose given once a day. If the second dose is given late in the afternoon (about 4:00 P.M.) the peak diuretic effect is reached well before bedtime, and the patient is assured a good night's rest. Comparable doses of hydrochlorothiazide and hydroflumethiazide are 100 to 200 mg. daily, again in divided doses. Benzydroflumethiazide in a dose of 5 mg. two to three times daily produces a maximal diuresis.

Toxicity

In the three years that these drugs have been used serious side effects have been minimal except in isolated cases of jaundice[1,2] due to hepatotoxic injury, in severe skin eruptions similar to those seen in past years with the sulfonamides, and in serious electrolyte depletion. Mild gastrointestinal disturbances such as nausea and/or vomiting are infrequent and almost absent with the newer thiazides now available, although it was unusual to find them even with chlorothiazide. Mild skin eruptions of a maculopapular type were seen in approximately 1.5 per cent of cases treated with chlorothiazide. No such rash has occurred with benzydroflumethiazide. One case of true hepatotoxic liver injury with jaundice occurred in our experience, a case of congestive failure treated with one of the earlier thiazides.

Our greatest problem, as should probably be expected, has been the production of electrolyte depletion. The development of mild to moderate hypochloremic alkalosis occurs in most cases, and does not pose any great problem. If moderately severe chloride depletion occurs, the diuretic effectiveness of the thiazides seems to lessen somewhat. Correction of this with ammonium chloride combined with a carbonic anhydrase-inhibitor rapidly restores the chloride and carbon dioxide combining power to normal, and effective diuresis is resumed. This program has been found useful in maintaining thiazide or mercurial effectiveness. Hyponatremia has not been a frequent effect. It seems most likely to occur in salt-depleted patients with severe liver or renal impairment or in the late stage of congestive heart failure. Occasionally a salt-losing nephropathy will be forced into hyponatremia by these drugs. Some type of severe metabolic disorder seems likely in most cases in which excessive sodium or potassium depletion occurs, and should be sought for at once if unusual depletion occurs. One such case occurring in one of our Sections of Medicine presented itself as a hypokalemic myopathy[3] with severe muscular weakness eventually causing actual paralysis. In this case severe potassium depletion occurring with chlorothiazide in a hypertensive patient caused a careful search to be made by her alert physicians resulting in the discovery of primary aldosteronism. Discontinuance of chlorothiazide resulted in improvement; the patient had discontinued therapy of her own accord. On reinstitution of the thiazide muscular weakness again occurred, but she improved on supplementary potassium therapy. On discontinuing the potassium she again developed such severe muscular weakness that she was unable to stand or hold her head erect. Such magnitude of potassium depletion is rare in the ordinary therapy of congestive failure, but lesser degrees do occur not infrequently in advanced cases of congestive failure with severe hepatic or renal dysfunction, or both. Benzydroflumethiazide seems to have produced less potassium depletion than other drugs mentioned above (FIGURE 1).

Digitalis intoxication and reduced tolerance of this drug for maintenance have seemed to occur more frequently in patients that are taking fairly large amounts of the thiazides continuously. This is especially true in advanced cardiacs in congestive failure and in elderly patients.

Several other interesting effects of these agents have been reported recently.[4,5] FIGURE 2 depicts the hyperglycemic effects of chlorothiazide and benzydroflumethiazide in a diabetic in congestive failure, on a fixed dietary intake, and not taking insulin or oral antidiabetic drugs. Hyperglycemia has been a rare occurrence in all our diabetics treated with thiazides, and it is concluded that it is not a usual effect. However, it may occur and produce difficulty in a diabetic patient's control. Speculation on its cause is not the aim of this presentation, and no doubt an answer is forthcoming in the near future.

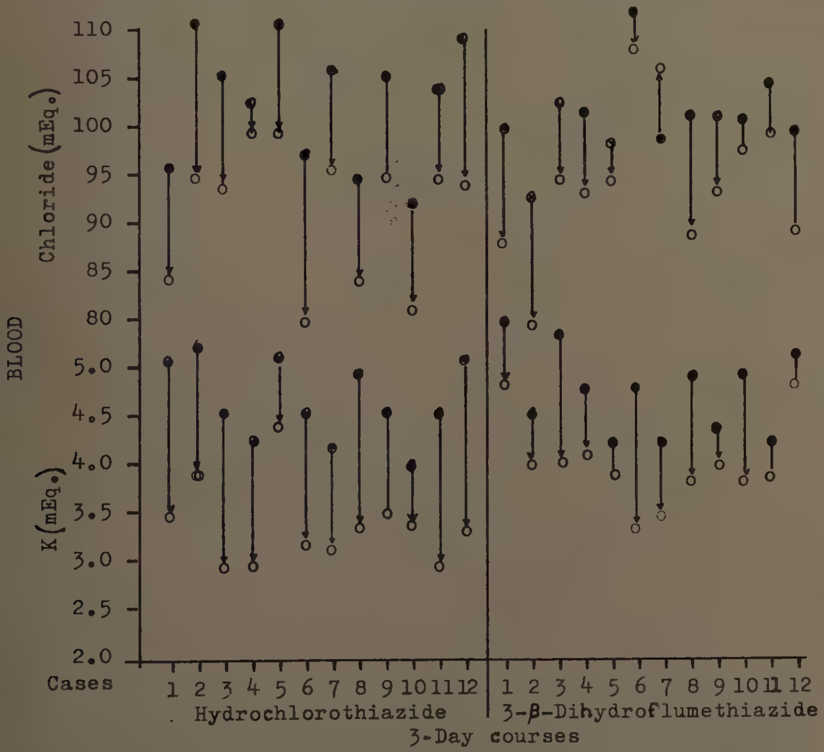

FIGURE 1. Effects of hydrochlorothiazide (50 mg. t.i.d.) and benzydroflumethiazide (5 mg. t.i.d.) on serum chlorides and potassium in 24 cases after each three-day course of treatment.

Despite the propensity of these drugs to produce an elevation of blood uric acid, they have not in our experience produced true gout except when a patient actually has had this metabolic disorder to begin with; in such a case thiazide may cause a real problem. FIGURE 3 shows the effects of chlorothiazide in a case of true tophaceous gout. After stabilizing the uric acid levels and the clinical manifestations of this particular case by appropriate therapy, the thiazide produced a striking rise in the blood uric acid, with reactivation of acute gout symptoms.

Refractoriness in Heart Failure

In addition to the correction of many factors that contribute to this condition, such as inadequate digitalization, electrolyte depletion, marked ascites and/or hydrothorax, the use of several agents that by themselves may not be considered diuretics may result in responsiveness produced by diuretic drugs. The agents are not always effective, but certainly are worthy of trial in such a situation.

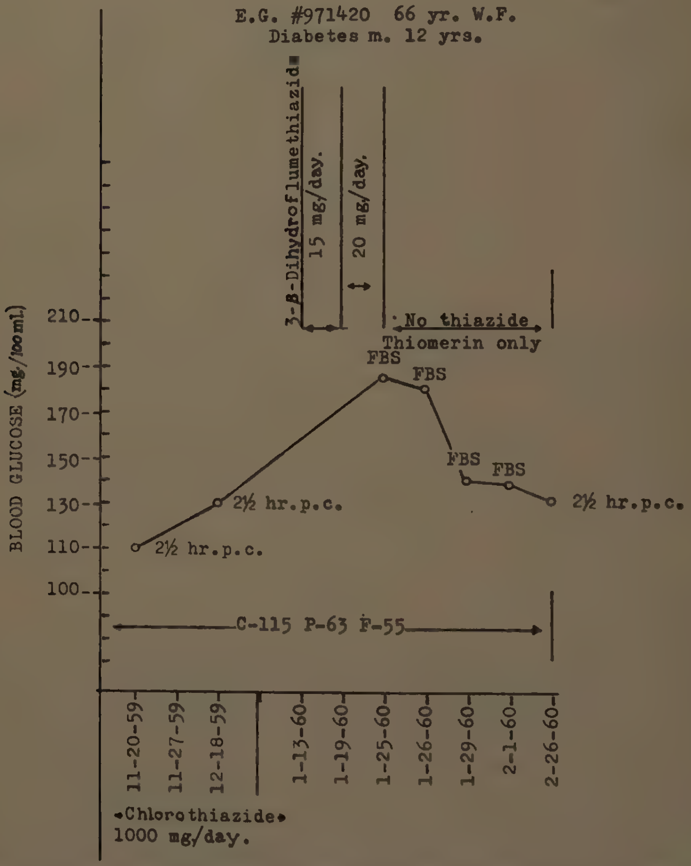

FIGURE 2. Hyperglycemic effects in a case of diabetes mellitus after administration of a thiazide.

Corticosteroids of the newer types such as prednisone, prednisolone, and triamcinolone are effective in producing diuresis in some cases when used in conjunction with mercurials, and/or thiazides after these latter drugs have failed to work effectively. Triamcinolone, particularly, seems to work well.

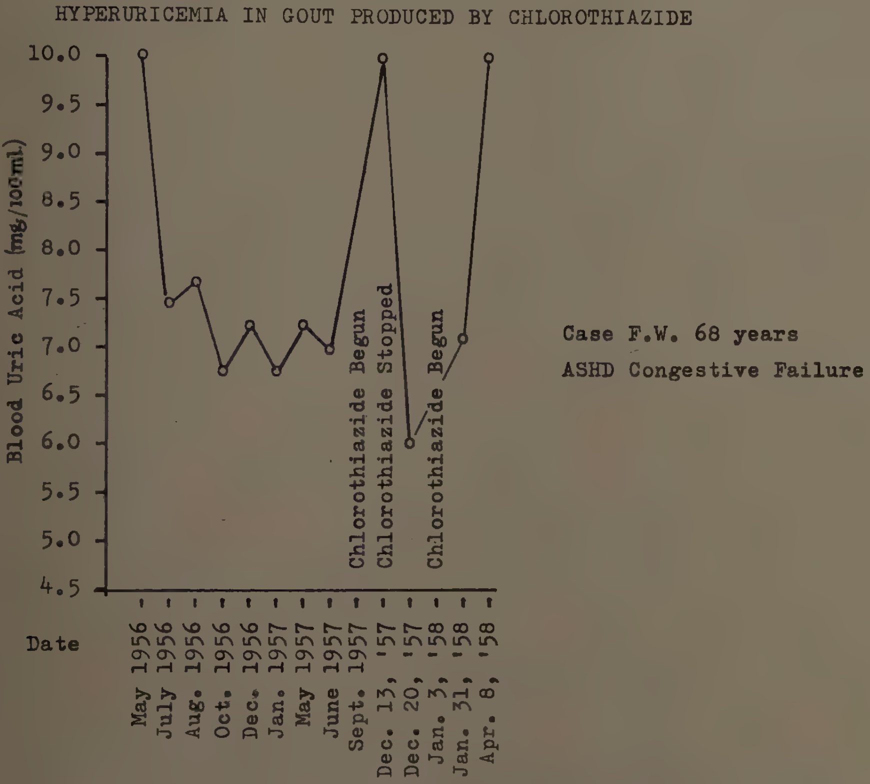

FIGURE 3. Effects of chlorothiazide on blood uric acid levels in a case of tophaceous gout.

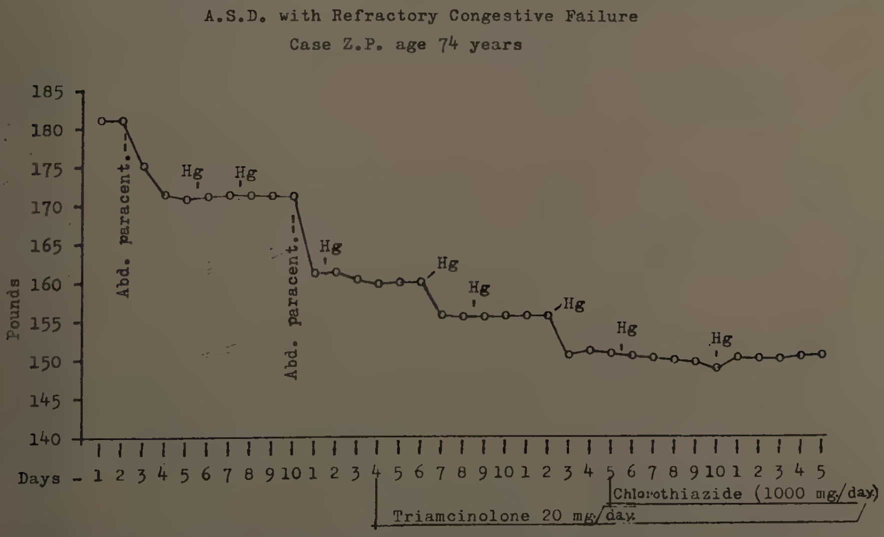

FIGURE 4. Case of refractory congestive heart failure, showing diuresis to mercurials and chlorothiazide after administration of an adrenocorticosteroid.

FIGURE 4 shows a case of refractory congestive failure treated with this material. This class of steroid compounds seems to augment natriuresis rather than retention of sodium, as cortisone and hydrocortisone do.

Spirolactones have recently been introduced for use in edema states to augment sodium excretion by their antialdosteronal activity. In refractory heart failure heavy dosage of such material does result in increased sodium excretion, but is more effective if combined with thiazides or mercurial administration. It has not proved as successful in terminal congestive failure states as in advanced cirrhosis with ascites, but it does afford the clinician an added mode of therapy for this condition and can be effective when other conventional therapy has failed. FIGURE 5 shows the use of SC 8109 in a case of refractory congestive failure, coupled with the use of a mercurial.[6] The excretion of salt in this particular case is more striking than the weight loss achieved, but does substantiate the effectiveness of this compound.

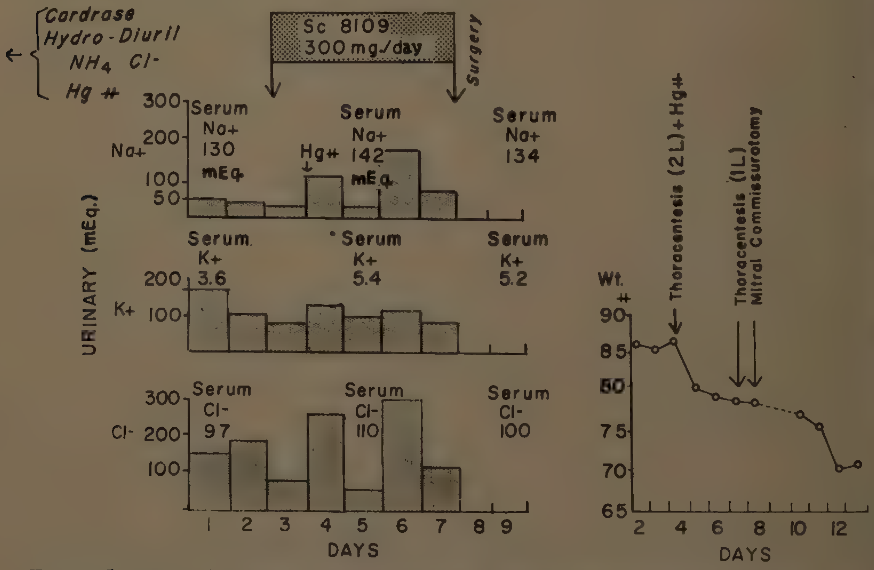

FIGURE 5. Case of refractory congestive heart failure treated with a spirolactone (SC 8109) showing increased sodium and chloride excretion.

Summary and Discussion

Experience with the different thiazide analogues has shown them all to be exceptionally good diuretic drugs. One of the latest, benzydroflumethiazide, is a very potent sodium-blocking agent that has excellent diuretic effectiveness. There are seemingly minimal side effects with these compounds. Electrolyte depletion of potassium has seemed less than with other drugs. Drug tolerance does not occur and the blocking effect on tubular sodium reabsorption is continuous. It is felt that these drugs should be given in the smallest effective doses necessary to achieve their purpose, and for as short a period of time as will maintain control of congestive failure.

All diuretic drugs are adjunctive in the control of edema in cardiac failure and are never used to supplant digitalis, salt restriction, and reduced physical activities. Some patients taking thiazide compounds can increase the salt intake even to normal amounts and still remain controlled, which is psychologically beneficial.

Diuretic effectiveness may fail for various reasons; however, electrolyte depletion and failure to maintain adequate glomerular filtration rate seem to be chiefly responsible. Dilutional hyponatremia possibly induced by excessive antidiuretic hormone activity in severe advanced congestive failure may be a serious and unrectifiable complication with the terminally exhausted myocardium. Hypochloremic alkalosis can usually be reversed, and true hyponatremia (salt depletion syndrome) can be restored with resultant diuretic effectiveness. Potassium deficiency must be suspected in any patient with unusual muscular weakness, paresthesia, exhasution, or digitalis intoxication. Metabolic causes of excessive potassium losses must be searched for. It is therefore mandatory to check serum electrolytes in patients receiving constant and heavy doses of these thiazide materials.

While unusual side effects of these drugs do occur, and they may seem to have been overemphasized here, the conclusion remains that they may occur but are infrequent. They are presented to call attention to possible causes of trouble that may seem inexplicable to the practitioner unaware of their potentialities.

The use of corticosteroids and aldosterone-blocking agents in refractory heart failure has been discussed for the purpose of pointing out that with the adjunctive use of thiazides or mercurials diuresis may be restored.

It is felt that the thiazide drugs approach the mercurials in potency, but do not exceed them except, because of their low toxicity and repetitive action, in controlling and stabilizing the edema state in long-term diuretic therapy. The low cost and the high patient acceptance of oral medication of this type rates them as ideal diuretics. It is difficult to concede that more potent agents will be more beneficial unless they will be entirely free of the chief undesirable side effects. Effective research may produce some compound that will selectively block sodium reabsorption and cause excretion of free water, and yet be free of the serious electrolyte depletion problem.

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CURRENT CONCEPTS OF THE MECHANISMS OF HYPERTENSION

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While problems concerned with the mechanisms responsible for experimental and secondary hypertension are germane to the topic, I shall direct my discussion to the knowledge and theories currently available about the cause of primary or essential hypertension.

Essential arterial hypertension is a syndrome in which there are probably a number of disorders, each with a different cause for the elevated blood pressure. For instance, until very recently patients with hypertension secondary to adrenal cortical adenomas secreting aldosterone and those whose elevated blood pressure is due to unilateral kidney disease were included in the essential hypertension group. Because of the diverse characteristics of individual patients with essential hypertension, it seems reasonable to conclude that there may be additional disease entities to be separated from the primary group.

Increased total peripheral vascular resistance[1] and an increase in the force of cardiac contraction[2] are consistent findings in patients with essential hypertension; occasionally, however, an increase in cardiac output partially or completely explains the hypertension noted.[3] Whether these latter patients have hypertension at different (perhaps earlier) stages or whether the increased peripheral vascular resistance indicates that the cause for the blood pressure elevation is different remains uncertain. There does not appear to be a systematic or general increase in blood viscosity in hypertensive patients.

The calculated peripheral vascular resistance increase is more or less evenly distributed over the various vascular beds except for the kidney where it is usually greater.[2] Relying heavily on observations made in animals with experimental hypertensions, it has been noted that the resistance occurs in the arterioles, in the region of the precapillary sphincters, and perhaps in the venules.[4] Changes in the volume and capacity of the capillary bed, as suggested by findings in nailfolds of hypertensive patients, may play a role in the elevation of blood pressure.[5]

The search for the mechanism causing increased peripheral vascular resistance has moved in several directions. Epidemiologic evidence suggests that genetic factors are very important in the development of hypertension. Without a detailed discussion, it can be pointed out that records of individual families,[6] studies of large groups of families,[7] and twin data[8] all support the hypothesis that inheritance plays an important role in the pathogenesis of essential hypertension. Pickering and his associates have interpreted these data, together with those that they themselves have collected, as showing that blood pressure, particularly in the upper ranges, is inherited as a graded characteristic.[9] They have pointed out that among patients with primary hypertension there is no evidence that high blood pressure is qualitatively different from normal blood pressure; in essence, the blood pressure distribution curve of the population is a feature that must be considered in the same way that height and weight are noted. Environmental factors in a society may shift the entire distribution curve up or down and, indeed, may make secondary hypertension more or less common.

The reaction to these ideas has been swift and various. Some investigators have categorically denied their significance. Several studies, by rearrangement of the original data and by the addition of other material, have demonstrated that, instead of the smooth bell-shaped frequency distribution curve originally observed, there is one with secondary peaks in the hypertensive range, even when patients with secondary hypertension are excluded.[10]

If Pickering's concept, which seems reasonable to me, is correct, it needs much more supporting data. Armstrong, Peterson, and I have observed recently that, in a group of normotensive and mildly hypertensive persons with no evidence of secondary hypertension, salt-losing was fairly well correlated with blood pressure in both the normotensive and hypertensive range.[11] There was no sharp line of demarcation between a "salt-loser" and a "nonsalt-loser" when blood pressure was considered. The salt-losing feature of the hypertensive may, then, be a graded nonqualitative characteristic—related only to blood pressure until secondary renal changes appear—rather than a unique characteristic of human hypertensive disease.

Other similar evidence may favor credence, but pristine and precise epidemiologic data are needed to offer the Pickering hypothesis positive support. If the hypothesis is correct, it may narrow the search for the cause of hypertension. It may then be asked what genetic factors cause the blood pressure to be higher in the upper end of the curve and also what predisposes these patients to have vascular hyperreactivity and early death. Physicians must also direct their attention to when and how "secondary" (possibly renal) hypertension augments this initial fault.

It is traditional to consider the increased peripheral vascular resistance an expression of either chronic vasomotor change, such as might be engendered by anxiety or resetting of baroreceptors, or of circulating pressor materials, or of both. Structural changes in small blood vessels that might account for increased resistance early in hypertension have not been studied in detail, although there is evidence that such changes may occur.[12]

Because most available evidence implicates vasomotor stimuli or pressor materials as the cause of the resistance change, I will now consider these.

Many areas in the brain influence vasomotor activity. Most of these are interrelated and few can be described accurately as centers, since they are so poorly localized and defined. The medullary center is a representative area that influences blood pressure. Its connections can be demonstrated by its responses to stimuli from the cortex, thalamus, respiratory centers, central and peripheral chemo- and baroreceptors, and humoral agents. Impulses from these central pressor areas travel through fibers of the sympathetic nervous system both to the cells around blood vessels and to the adrenal medulla where they apparently cause the release of norepinephrine and epinephrine.[13]

It is apparent that a sustained increase in vasomotor tone might be caused by increases in the number of afferent impulses to central pressor areas from the baroreceptor centers or from cortical stimulation. Widespread speculation that a resetting upward of aortic arch and carotid body baroreceptors, causing blood pressure to be maintained at a higher level, might occur in human hypertensives, has followed the demonstration in animals that the high output hypertension caused by section of carotid sinus and depressor nerves is accompanied by increase in peripheral vascular resistance.[14] It is not possible to assess the importance of this mechanism in initiating hypertension at this time, but the likelihood that it is the sole factor responsible is remote, since neurogenic blockade will not lower blood pressure to normal in most patients with essential hypertension. That it may play a role in chronic hypertension has been suggested by the observation that patients successfully treated with drugs causing a blood pressure fall to normal sometimes have a prolonged remission when the medicaments are discontinued.[15]

The ability of emotional stimuli to alter blood pressure acutely is responsible for a great body of literature about the role of the central nervous system in the pathogenesis of essential hypertension. Several experiments have suggested that such stimuli may cause chronic blood pressure elevation in man, but the evidence that this is the primary defect in essential hypertension is not convincing. Pertinent literature of the Union of Soviet Socialist Republics, recently reviewed by Simonson and Brozek,[16] is dominated by the theory that central nervous system stimulation is the primary defect in essential hypertension. Soviet investigators have compiled impressive experimental documentation to support this concept. Many of their therapeutic efforts are directed to relief of this neurogenic disorder, but neither their results nor their experimental evidence do more than make this hypothesis an attractive possibility.

It is expedient only to acknowledge the possibility that a variety of humoral agents may initiate essential hypertension. Experimental and clinical examples demonstrate that lack of,[17] excessive amounts of,[18] or imbalances of normally occurring materials[19] or new hormones[20,21] may produce hypertension. These endocrine defects arise from abnormalities in the adrenal medulla and cortex, the kidney, the liver, and the brain. The role of renal ischemia and renal pressor mechanisms in the production of human renal hypertension now seems reasonably secure. Recent studies demonstrate conclusively that removal of a diseased kidney relieves hypertension in man, although limitations of the procedure are not well understood. Whether the renal ischemia and the renin-angiotensin II system operate as primary factors in essential hypertension will not be settled finally until better angiotensin assay methods are developed, or until the cause is found elsewhere. Because of the similarity between experimental renal hypertension and the essential variety of man, it is conceded by many (but not proved) that renal pressor systems may help maintain blood pressure in the chronic stage. This is supported by the observation that angiotensin II has been identified in the blood of some, but not all, patients with severe hypertension.[22]

That dietary factors might be responsible for hypertension is an old hypothesis. Excesses of salt have attracted much attention in this regard since experimental hypertension may readily be produced in some species by this means.[23] The observations of Dahl and Love[24] on the relationship between salt consumption and blood pressure levels and several epidemiological studies that demonstrate that hypertension is prevalent in areas of the world where salt consumption is high tend to implicate this substance in the development or perpetuation of the disease. Other abnormalities, such as the salt-losing characteristic of hypertensives and the elevated serum sodium in hypertensives reported by some,[25] leave little doubt that salt metabolism is altered in many persons with high blood pressure. It is not clear how sodium excess causes hypertension in animals. It is possible that it occurs when penetration of cells by increased amounts of sodium ions causes either swelling of blood vessel cells or enhanced reactivity to normal stimuli and increased peripheral vascular resistance.[2] If salt excess is a pathogenic factor in essential hypertension, it probably operates through and in conjunction with hormones of the adrenal cortex, chiefly aldosterone. Therapeutic successes with diuretics and low salt diets have enhanced interest in the role of sodium in the development of hypertension. Evidence available, however, favors the view that defects in sodium metabolism are secondary in human essential hypertension.

Mendlowitz *et al.*[26] have proposed an interesting hypothesis of the genesis of primary hypertension that permits correlation of these several factors. By measuring the "work of constriction" in the digital circulation in different circumstances, these investigators concluded that the vasoconstriction of patients with essential hypertension is actually due to the hypersensitivity of the blood vessels to normal discharge of norepinephrine. By deductive reasoning they have implicated as a cause of primary hypertension a deficiency of O-methyl transferase, one of two enzymes that inactivate norepinephrine. Mendlowitz has suggested that this deficiency may be an inborn error of metabolism, which would explain the aggravation of hypertension by emotional factors and its amelioration by factors that block nerve impulses and render infused norepinephrine less potent. As noted, it would not preclude the contribution of renal or other factors to the primary defect, late in the disease, when *arterio-* and *arteriolo*sclerosis have made their appearance.

In conclusion, recent developments support the hypothesis that genetic factors are responsible for the initial defect in many patients with recognized essential hypertension. This deficit apparently produces vascular hyperreaction as one of its important functions. On this foundation of hyperreaction, a variety of dietary, hormonal, and neurogenic factors interact to raise blood pressure and peripheral vascular resistance. Eventually (although perhaps early) arterio- and arteriolosclerosis develop, ischemia of tissue occurs, and secondary hypertension is superimposed on the primary vascular defect.

Admittedly such a view of the pathogenesis of essential hypertension is oversimplified and narrow. Nevertheless, such ideas, if not held too rigidly, may provide the framework for eventual understanding and solution of the problem.

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PATHOLOGY OF HYPERTENSION

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Essential hypertension manifests itself as a generalized disease of the vascular system including the myocardium. One is apt to lose sight of this fact due to the spectacular lesions that can be demonstrated in certain target organs namely the heart, the brain, and the kidneys.

Morphologically, the effects of hypertension are manifested chiefly in the small arteries and arterioles of the heart, brain, and kidneys. In 2597 fatal cases reviewed by Clawson (1941), death was attributed to myocardial insufficiency in 43 per cent, to coronary artery disease in 36 per cent, to cerebral hemorrhage in 14 per cent, and to renal insufficiency in 7 per cent. Therefore patients with essential hypertension will most often succumb to either heart failure or hypertensive encephalopathy with cerebral hemorrhage.

Pathology of the Heart

Even when the major burden falls elsewhere, hypertensive patients show some degree of cardiac pathology at the post-mortem table.

In essential hypertension the striking feature is concentric cardiac hypertrophy, which is a constant finding. The first effect on the heart is left ventricular hypertrophy; subsequently with progressive disease there is seen right ventricular hypertrophy. With supervening cardiac failure, the cardiac chambers are dilated with hypertrophy of all the walls. The heart weight usually exceeds 500 gm. The papillary muscles of the left ventricle become hypertrophic while the interventricular septum impinges on the right ventricular cavity. The endocardium is characterized by grayish-white flecks of fibrosis (FIGURE 1).

Histologically the myocardium is characterized by an increase in the size of the individual muscle fibers (Gould, 1952). The cell nuclei also increase in size while demonstrating varying degrees of pleomorphism. There is also noted a diminution in the number of arterioles and capillaries of the myocardium. Focal areas of fibrosis are scattered through the myocardium, particularly in the anterior wall of the left ventricle and in the interventricular system.

The coronary arteries show atherosclerosis of varying severity.

Pathology of the Small Arteries and Arterioles

The lesions of essential hypertension are confined to the small arteries and arterioles where the greatest pressure gradient in the circulation occurs. These vessels measure less than 100 μ in diameter. It must be emphasized that the vascular changes to be described affect all the arteries and arterioles of the body. There are, however, variations in the susceptibility of the vasculature of different organs to this disease. The kidney is the most susceptible, but the myocardium, brain, adrenal glands, pancreas, gall bladder, and intestines are also affected.

Four chief types of arteriolar lesions are noted in essential hypertension, depending on the time of onset, duration, and severity of the disease. These lesions may be classified in order of increasing severity as arteriolar spasm, arteriolar hypertrophy, arteriolar fibrosis, and arteriolar necrosis.

Arteriolar Spasm

The first physiological response to the internal stress of hypertension is spasm of the arteriole. Sommers and his associates (1958), in a recent study of renal biopsy material, have shown that the first change occurring in the arterioles of the hypertensive is an abnormal concentric overlapping of normal-appearing smooth muscle cells that make up the arteriole walls. This morphological change in the wall of the arteriole was inferred to be spasm. On a control series of 12 kidney biopsy specimens removed for diagnostic purposes in normotensive individuals, this change was noted only once.

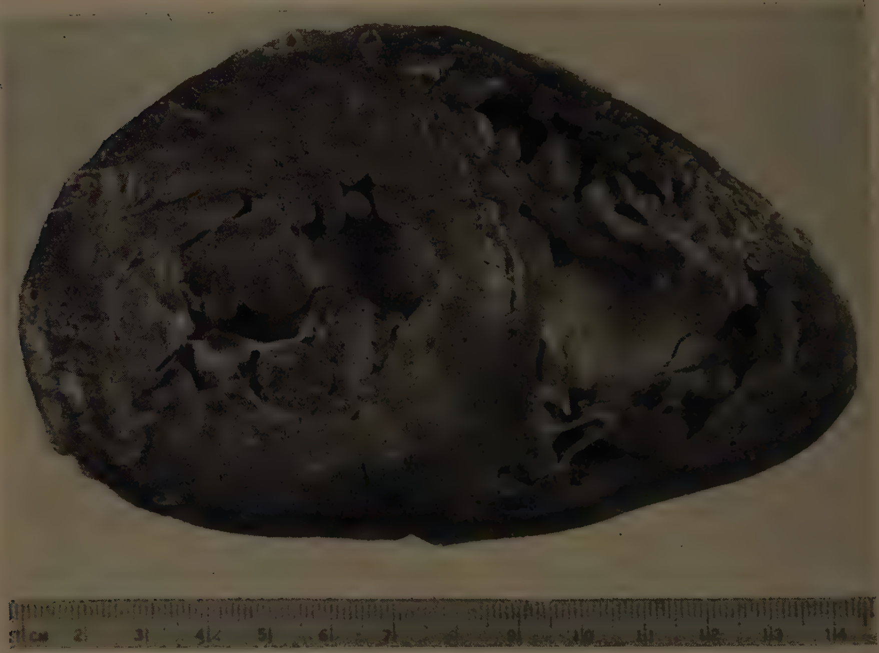

FIGURE 1. Concentric hypertrophy of the heart in essential hypertension.

Arteriolar Hypertrophy

With continuing stress the small arteries and arterioles respond by proliferation of the endothelial cells and subendothelial connective tissue, reduplication of the internal elastic lamina, hypertrophy of the smooth muscle fibers of the media, and the formation of new musculoelastic fibers (FIGURE 2). This hypertrophic picture is identified by a concentric laminated pattern, also known as the "onion-skin" appearance of the arterioles. These changes are not dissimilar to changes seen during the physiological growth of arteries during the first several years of life.

A comparable histological picture is also noted in the pulmonary vasculature when pulmonary hypertension has supervened due to either congenital or acquired valvular heart disease. This type of lesion in the arteriolar bed suggests hypertrophy in the face of excessive strain.

With the continued stress of hypertension the arteriolar walls begin to undergo degenerative changes. The commencement, distribution, and severity of these changes vary as to the duration and clinical cause of the disease. Again it must be emphasized that the degenerative process occurring in the arteriolar bed is generalized but is best demonstrated in the interlobular arteries and the glomerular afferent arterioles of the kidney.

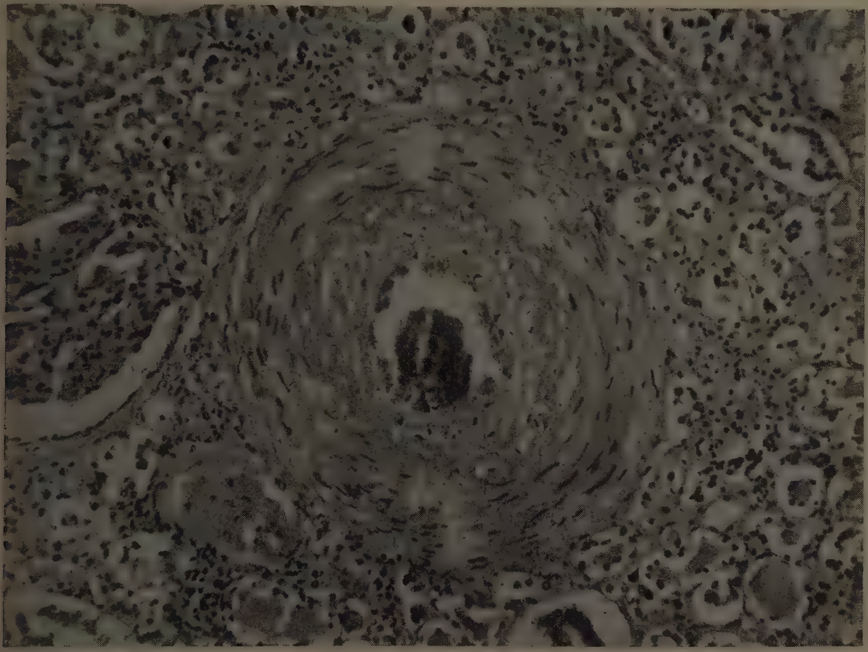

FIGURE 2. Arteriolar hypertrophy. Note subintimal connective tissue proliferation, reduplication of internal elastic lamina, and hypertrophy of smooth muscle of media.

Arteriolar Fibrosis

The degenerative process of fibrosis is characteristic of essential hypertension and is of slow evolution. The vascular walls become thick and fibrotic, causing marked narrowing of the lumens (FIGURE 3). The vascular fibrosis arises from the subintimal region and eventually obliterates the muscularis, causing complete loss of underlying cellular detail.

The arteriolar thickening is identified by a homogeneous collagenous thickening of the arteriolar walls. This type of vascular change affects all the small arteries and arterioles of the body, with varying degrees of susceptibility of different organs. The kidney seems to be the most sensitive to this type of alteration, but the vessels of the myocardium, brain, adrenal glands, pancreas, gall bladder, and intestines are also affected (Moritz and Oldt, 1937).

Arteriolar Necrosis

Arteriolar necrosis is a characteristic lesion in severe hypertension and may be regarded as a pathognomonic post-mortem sign that hypertension was present during life. It takes place in vessels where, owing to rapidly rising hypertension, there has been insufficient time for the arteriolar wall to thicken. In 97 per cent of cases it affects a considerable number of the glomerular afferent arterioles of the kidney, and is common in the vessels lying in the peri-adrenal fat and in the adrenal cortex. There is swelling, starting under the intima of the whole arteriolar wall, which eventually becomes replaced by a hyaline, eosinophilic structureless material containing, in the early stage at least, an appreciable quantity of lipoid (FIGURE 4). At various points along its length, plasma and blood cells are forced into the weakened degenerated wall as minute dissecting hemorrhages. Cellular proliferation around the lesion may develop, and a histological picture similar to that seen in polyarteritis nodosa may develop. The lumen of the vessel is slowly occluded. The process starts abruptly at the origin of the vessel from the interlobular

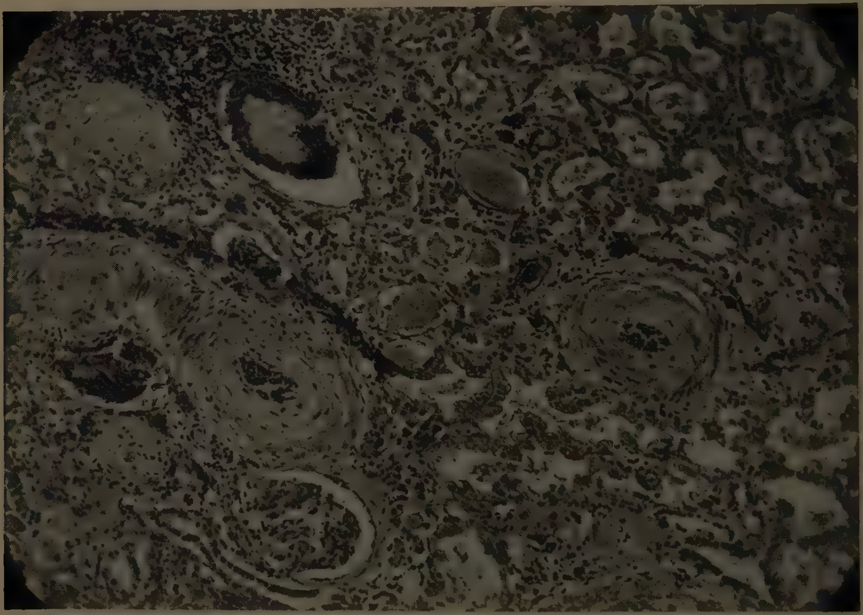

FIGURE 3. Arteriolar fibrosis. Note the thick and fibrotic walls, causing narrowing of the lumens.

artery and spreads toward the glomerulus, eventually involving its whole length. Necrotizing changes are frequently seen in the vessels of skeletal muscles, the adrenal glands, the pancreas, and the liver.

These degenerative features resemble closely the fibrinoid changes seen in diseases such as rheumatic fever, polyarteritis nodosa, and lupus erythematosus disseminatus, which are generally thought to be states of altered reaction, or of hypersensitivity.

This lesion has been frequently observed in animals in which severe degrees of hypertension have been induced experimentally; it may arise in the course of a few days. As it may be safely assumed that in these animals the vessels were normal before the experiment, it is very probable that the changes found are the direct mechanical consequence of high tension on the arteriolar walls.

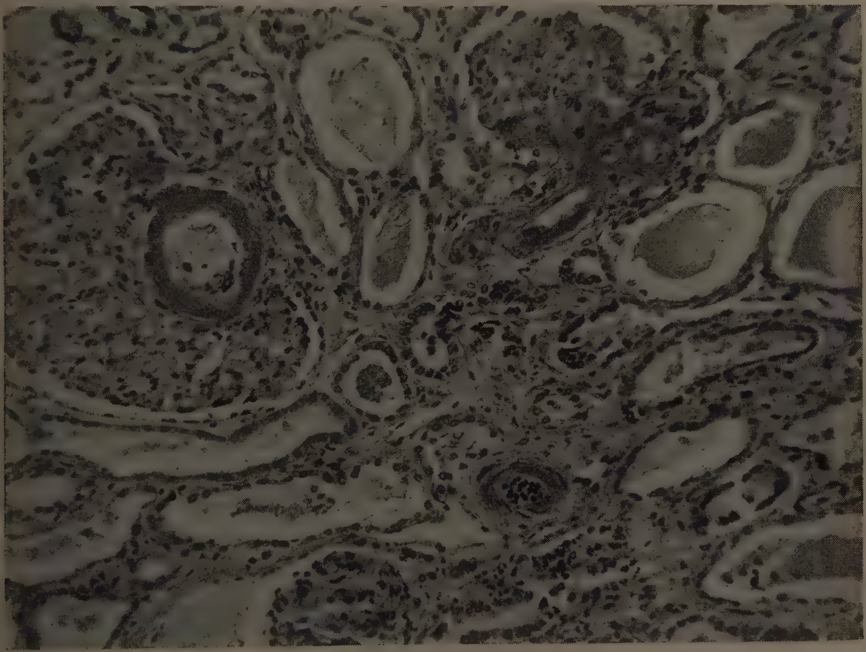

FIGURE 4. Arteriolar necrosis. Replacement of arteriolar wall by fibrinoid.

Kernohan *et al.* (1929), in an attempt to show that there were common features in the small arteries and arterioles in various organs and tissues of patients with hypertension, excised portions of the pectoralis major in a series of 53 hypertensive patients. They determined in histological sections the average ratio of the thickness of the arteriolar walls to the diameter of the lumen. The normal average was 1:2. In hypertensives the figure varied from 1:1.4 to 1:1.1, the variation being proportional to the severity of the disease.

Several years later, Morlock (1939) made a histological study of the arteriolar bed of the liver, pancreas, spleen, and the gastrointestinal tract of normotensive and hypertensive patients. He established that there are no changes in ratio as a result of increasing age. Marked thickening of the arteriolar wall and reduction of the ratio of wall to lumen, as compared with the normal ratio, were noted in hypertensive patients. He therefore obtained results similar to those previously found in the arterioles of striated muscle, and a similar variability with the severity of the disease.

The results of these histological studies emphasize that there exists a diffuse lesion of the arteriolar bed associated with hypertension.

This lesion, causing a restriction of the blood supply to the various tissues and organs of the body, is followed by degenerative changes of the parenchyma, fibrosis, and atrophy, leading to gradual failure of certain organs, notably the heart, the brain, and the kidneys. With failure of the heart there is cardiac failure or myocardial infarction; with failure of the brain, atrophy and hemorrhage; and with failure of the kidney, there is uremia.

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NEWER BIOCHEMICAL APPROACHES TO THE TREATMENT OF HYPERTENSION

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Most of the antihypertensive drugs in current use are products of pharmacological screening programs in animals. Even so, the limitations of this approach are frequently discussed and are reflected by the large number of "dead" drugs that have resulted from such programs. The need for improved screening techniques and the desirability of discovering other bases for the development of new antihypertensive drugs is apparent.

An approach that has interested us is a fundamental biochemical one consisting of the induction of alterations in the formation and degradation of aromatic amines in man and studying the biochemical and physiological effects. Actually, it is tempting to suppose that an elevated level of pressor amine(s) is involved in the hypertensive process itself. While this is obviously the case in patients with pheochromocytoma, no convincing data to support this supposition has been obtained thus far in patients with essential hypertension. However, with increased knowledge of the biochemical processes involved in amine metabolism it has become possible to manipulate tissue levels of amines in patients. This has led to the discovery of compounds with antihypertensive actions that often had not been observed previously in animal studies.

Three major processes are involved in the metabolism of the aromatic amines including phenylethylamine, tyramine, the catecholamines, tryptamine, and 5-hydroxytryptamine (serotonin):

(1) In each instance, synthesis is accomplished by the decarboxylation of an aromatic amino acid. Inhibition of the decarboxylation might be expected to result in a decreased synthesis of the amines; compounds with this property will be discussed subsequently.

(2) While alternate pathways exist for the enzymatic inactivation of some of the aromatic amines, oxidative deamination by monoamine oxidase (MAO) leading to an acid metabolite is important in each case. Many MAO inhibitors have been developed which, on administration to animals, lead to an accumulation of tissue amines.

(3) The other mechanism of amine inactivation, that of storage in tissues, is under active investigation in many laboratories. It is likely that blood pressure-lowering properties of the *Rauwolfia* alkaloids and certain newer synthetic analogues are mediated by an interference with mechanisms of storage in tissues. The discussion here will be restricted to MAO and decarboxylase inhibitors.

Monoamine Oxidase Inhibitors

A systematic investigation of the biochemical and physiological effects of MAO inhibitors in patients with hypertension was begun in our laboratory in 1957. Postural hypotension was known to be a frequent effect of iproniazid administered to psychiatric patients. The circumstance of blood pressure-lowering by a drug that also produces increased tissue levels of amines such as norepinephrine constituted an intriguing paradox. Methods were developed for measuring MAO inhibition in man so that the relationship to blood pressure changes might be determined. The first method resulted from the finding that serotonin could be fed safely to patients and was largely excreted in the urine as its MAO metabolite, 5-hydroxyindoleacetic acid (5-HIAA). A decreased excretion of 5-HIAA after administration of an arbitrary dose of serotonin (usually 20 mg.) afforded an index of MAO inhibition by a drug.[1] A simpler test resulted from the realization that if an amine was completely dependent on MAO for its metabolism, MAO inhibition would result in elevated excretion of amines which accumulate in the body as a whole or, possibly, in the kidney only. Using MAO inhibitors as biochemical tools in man, it was possible to show an elevated urinary excretion of many amines in patients.[2,3] Measurements of urinary tryptamine afforded a convenient index of MAO inhibition in man.[4]

The first MAO inhibitor studied, β-phenylisopropylhydrazine (JB-516, Catron), was known to be a pressor agent in the dog and thus was made available chiefly for "biochemical" purposes. It was found to be a potent hypotensive agent as well as an enzyme inhibitor in human hypertensives.[5] Inhibitors studied subsequently include nialamide (Niamid), phenelzine (Nardil), tranylcypromine (SKF-385, Parnate) and serine-N^2-isopropylhydrazide (RO-4-1038). The administration of each of these drugs to hypertensives was found to produce a marked rise in urinary tryptamine as well as a decrease in blood pressure, most marked in the standing position. Initially it was thought that administration of nialamide did not produce lowering of blood pressure. However, when large doses (300 to 500 mg./day) were administered, a blood pressure effect was observed. Favorable results have been reported recently of the use of nialamide given with chlorothiazide in hypertension.[6] The most potent and uniformly effective agent in our studies has been Catron. Toxic effects on the eye in several patients, however, has led to a severe curtailment of its use. Continued study of this class of compounds in hypertension is warranted for two reasons: (1) their property of producing mood elevation is quite useful in some cases and is unique among antihypertensive drugs, and (2) the actions on the autonomic nervous system are of a rather pure sympatholytic type and give minimal evidence of parasympathetic-blocking effects.

Is the blood pressure-lowering effect of these drugs due to inhibition of MAO? While increases in urinary tryptamine in our studies did not correlate precisely with blood pressure effects, the fact that all these compounds have both effects in man suggests a connection between them. Of several possible mechanisms that might mediate postural hypotension only two of those that have been considered will be mentioned here.

One is the accumulation of dopamine, the precursor of norepinephrine. Dopamine is a good substrate for MAO and is a depressor agent in some species. However, when dopamine was infused in human subjects, a pressor response was observed that was potentiated by MAO inhibitors.[7] Since dopamine is a weak pressor agent, however, it could be argued that excess dopamine might compete with norepinephrine at receptor sites and result in a lowering of blood pressure during standing.

The other mechanism, one for which good evidence has been obtained, is that of sympathetic ganglion blockade. Gertner[8] reported that perfusion of MAO inhibitors into the superior cervical ganglion of the cat markedly decreased the effects of preganglionic stimulation on the nictitating membrane. In studies in the intact dog and cat, Goldberg and DaCosta[9] found that large doses of iproniazid and harmine given intravenously produced sympathetic blockade, transmission through parasympathetic ganglia being unaffected. The question arises whether some amines, metabolized normally by MAO, might accumulate at the ganglion or in sympathetic nerves after enzyme inhibition and interfere with transmission. Gertner *et al.*[10] have reported that serotonin appears in the perfusate from the isolated cervical ganglion after perfusion with iproniazid. Since Trendelenberg[11] has demonstrated that serotonin facilitates transmission through the superior cervical ganglion of the cat, it is conceivable that the amine normally plays a role in ganglionic transmission. Thus, while interaction with serotonin or other amines in sympathetic ganglia or nerves is possible, further studies are required to determine whether this is simply in the nature of pharmacological antagonism or is related to enzyme inhibition.

Decarboxylase-Inhibitors

A number of compounds have been shown to inhibit aromatic amino acid decarboxylation *in vitro* and *in vivo* in animals.[12,13] The compound selected for administration to humans was α-methyl-3,4-dihydroxy-DL-phenylalanine (α-methyl-dopa). This compound was synthesized by G. A. Stein and K. Pfister, of the Merck Institute, Rahway, N. J., and was found to be a competitive inhibitor of dopa decarboxylation *in vitro* by Sourkes in 1954.[13] Although the compound produced no striking pharmacological effects when injected into animals, its ability to block decarboxylation *in vivo* could be shown pharmacologically. Dengler and Reichel[14] reported in 1958 that pretreatment with α-methyl-dopa blocked the pressor effect of dopa in the spinal cat and the depressor effect in the guinea pig. Similarly, Westermann *et al.*[15] showed that the bronchoconstriction produced by the serotonin precursor 5-hydroxytryptophan in guinea pigs and the central excitation it produced in mice were prevented by pretreatment with α-methyl-dopa. Goldberg *et al.*[16] have found that increments in heart contractile force produced by 10 to 20 mg./kg. intravenously of L-dopa or DL-metatyrosine in the dog are completely inhibited by pretreatment with 100 to 200 mg./kg. of α-methyl dopa. Westermann and his associates[15] also presented biochemical evidence that 5-HTP decarboxylase and dopa decarboxylase might be identical. From recent studies of purified enzyme preparations Udenfriend *et al.*[17] concluded that a single enzyme might be responsible for all aromatic amino acid decarboxylations.

It was decided to determine whether evidence of decarboxylase inhibition by α-methyl-dopa could be found in man. At this time a report by Smith[18] described decreases in brain and intestinal serotonin of mice following repeated injections of 400 mg./kg. α-methyl-dopa. Because of the large doses required to induce amine changes in these experiments, doses of 1 to 2 gm. were used in our patients even in initial studies, in the hope of producing biochemical changes.

The decarboxylations of four different amino acids were investigated in hospitalized patients with essential hypertension. These were tyrosine→tyramine, tryptophan→tryptamine, dopa→dopamine and 5-HTP→serotonin. The technique used was to administer the amino acid orally or intravenously and to evaluate the extent of its decarboxylation by measuring the amount of the corresponding amine excreted in the urine during the following 8 hours. After control measurements were made, each study was repeated during the administration of α-methyl-dopa, a single 2.0-gm. dose of the inhibitor being given orally 2 hours prior to the administration of the amino acid. As described in detail elsewhere by Oates *et al.*,[19] administration of α-methyl-dopa resulted in a marked decrease in the quantity of amine excreted following each amino acid. The percentage inhibition produced was in the range of 50 to 80 per cent.

TABLE 1

EFFECT OF α-METHYL-DOPA* ON LEVELS OF URINARY 5-HYDROXYINDOLES IN PATIENTS WITH CARCINOID

Compound	Case no.	Control† (mg./day)	During α-methyl-dopa†
5-HIAA	1	635	182
	2	540	198
	3	55	30
	4	87	65
	5	944	929
Serotonin	3	24	7
5-HTP	1	<1	52
	2	8	52
	3	18	44
	4	<1	<1
	5	<1	ca. 1.2

* Four to 6 gm./day.

† Values are averages of at least 3 determinations.

To obtain additional evidence of the biochemical effects of α-methyl-dopa in man, the compound was administered to patients with malignant carcinoid and pheochromocytoma. Some of the chemical changes observed in carcinoid are summarized in TABLE 1. In three of these patients (Cases 1 to 3) the inhibition of 5-HTP decarboxylase was shown convincingly. In addition to a decreased excretion of 5-HIAA, there was an increased excretion of 5-HTP, reflecting accumulation of this precursor in the body. The patient in Case 3 had a greatly elevated urinary excretion of serotonin, which was also decreased during treatment with α-methyl-dopa. In Case 4 a moderate decrease in the excretion of 5-HIAA occurred, and in Case 5, in which 5-HIAA values were as high as 1.0 gm./day, there was no detectable effect. In the last case the agent may have been poorly absorbed from the intestine, since the patient had severe diarrhea. Two patients with pheochromocytoma were studied by

J. Richard Crout, of our section; a significant decrease (average, 30 per cent) in the excretion of catecholamine metabolites occurred during administration of α-methyl-dopa.

It was noted even in the first experiment in man that inhibition of decarboxylation by α-methyl-dopa was accompanied by pharmacological effects. These consist chiefly of postural lowering of the blood pressure and sedation. Therefore the compound was evaluated as a possible therapeutic agent in hypertension. The results of these studies are presented elsewhere in this monograph by L. Gillespie. In a large group of patients with various disorders the central effects have occurred consistently during the first 48 to 72 hours of treatment, but have diminished markedly thereafter. It is our impression that subtle effects, best described as tranquilization, persist in most patients during continued treatment. The lowering of blood pressure, most marked with the upright position, was observed in the carcinoid patients also and, with the exception of Case 1, limited the daily dose that could be administered to 4 to 5 gm./day. Therapeutic results in carcinoid patients are as yet inconclusive. Definite moderation of flushing was observed in Cases 1 to 3, in Case 4 the patient was relatively asymptomatic, and in Case 5 flushing was unaltered. Diarrhea was a prominent symptom in Cases 1 and 5, but was not altered significantly by treatment.

These preliminary findings in man are of sufficient interest to warrant evaluation of α-methyl-dopa as a therapeutic agent in mental disease, hypertension, and disorders characterized by a relative or absolute excess of aromatic amines. Furthermore, it is important to ascertain whether the pharmacological effects of the agent are due to decarboxylase inhibition. Study of other decarboxylase inhibitors may be required to determine this. Experiments by S. Udenfriend and his associates (personal communication, 1960) and by C. C. Porter and L. S. Wilson (personal communication, 1960) in guinea pigs, rats, and mice suggest that, in addition to a depletion of amines by blockade of synthesis, α-methyl-dopa and related compounds may act on the storage mechanism as well. The decline and recovery of brain serotonin after single doses of α-methyl-dopa were found to occur over a period of several hours, and paralleled changes in brain decarboxylase activity. However, depletion of cardiac and brain norepinephrine persisted up to 72 hours and was maximal even after decarboxylase activity had returned to normal and the inhibitor had disappeared from the tissues. It is reasonable to speculate that the sedation and reduction in standing blood pressure produced by α-methyl-dopa in man are related to reduced levels, respectively, of serotonin in the brain, and of norepinephrine in the sympathetic nervous system. Careful studies correlating the pharmacological and biochemical effects in laboratory animals and in patients will undoubtedly clarify the problem.

Summary

The thesis of this report is that new antihypertensive agents may be discovered on the basis of their inhibiting biochemical processes involved in the metabolism of aromatic amines. In the case of agents of this type, pharmacological studies in animals often have not been reliable in predicting blood pressure-lowering actions in man. The monoamine oxidase inhibitors repre-

sent one example of this. Another is indicated by recent studies with an inhibitor of aromatic amino acid decarboxylase, α-methyl-dopa.

Acknowledgment

The following investigators participated in the work presented: J. A. Oates, L. Gillespie, Jr., J. R. Crout, and L. Goldberg, of the Section on Experimental Therapeutics, and S. Udenfriend, of the Laboratory of Clinical Biochemistry, National Heart Institute, Public Health Service, Bethesda, Md. Generous supplies of α-methyl-dopa (MK-350) were available through the courtesy of E. Alpert and his associates, of Merck Sharp & Dohme Laboratories, Rahway, N. J.

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PHARMACOLOGICAL CONSEQUENCES OF SELECTIVE DEPLETION OF CATECHOL AMINES BY ANTIHYPERTENSIVE AGENTS

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Most hypotensive agents interfere with the functioning of the sympathetic nervous system in one of several ways: (1) the action of norepinephrine released at nerve endings may be inhibited (adrenergic blockade); (2) the flow of nerve traffic in sympathetic nerves may be reduced by suppressing central sympathetic centers (central adrenergic blockade); (3) the flow of sympathetic traffic may be reduced by blocking peripheral autonomic ganglia; and (4) chemical sympathectomy may be produced by making norepinephrine unavailable at sympathetic nerve endings, either by depleting the catechol amine stores, or by preventing the release of the amine by a nerve impulse. This paper concerns compounds in the latter category.

Rauwolfia Alkaloids

Reserpine and other *Rauwolfia* tranquilizing agents were at first thought to lower sympathetic tone by decreasing the activity of sympathetic centers in the central nervous system. This view was a logical one, since reserpine depletes norepinephrine stores in the brain. Carlsson *et al.*[1] were the first to note that reserpine releases catechol amines from peripheral tissues as well as from the brain, and they suggested that the cardiovascular responses to reserpine might be due, in part, to the loss of the transmitter at peripheral nerve endings. Thus after the injection of large amounts of reserpine into rabbits and cats, the peripheral sympathetic system does not operate.[1] As a result, ganglionic stimulants such as tetramethylammonium or nicotine do not raise blood pressure but, in fact, may lower it, while ganglionic depressants such as tetraethylammonium do not lower blood pressure.[2] In addition, electrical stimulation of sympathetic nerves fails to induce tachycardia[3] and a rise in blood pressure.[4] Moreover, the pressor effects of administered norepinephrine are enhanced.[5] Recently Burn and Rand[6] reported that reserpine depletes norepinephrine from arterial walls so that nicotine no longer constricts arteries by the local release of catechol amines.

It is not generally appreciated, however, that reserpine, in small doses, can lower blood pressure and release most of the peripheral norepinephrine without producing sedation or measurably affecting the content of brain norepinephrine or serotonin. A far greater separation of peripheral and central effects is attained with syrosingopine (Ciba). This carbethoxy analogue of reserpine has been shown by Plummer *et al.*[7] to lower blood pressure in nonsedative doses. Injected intravenously into rabbits, reserpine and syrosingopine are equally active in releasing heart norepinephrine; 25 μg./kg. of either drug completely depletes the catechol amines from the heart without appreciably lowering the levels of norepinephrine or serotonin in the brain. However, with increasing doses of reserpine there is a progressive decline in brain amines; a 50 per cent loss is induced with 100 μg./kg. of reserpine and almost complete loss with 800 μg./kg. In contrast, 500 μg./kg. of syrosingopine produces little decline in the content of brain amines, and 800 μg./kg. depletes the brain amines by 50 per cent.[8] Correspondingly it takes about eight times as much syrosingopine as reserpine to produce sedation. Thus the range of doses over which syrosingopine depletes heart norepinephrine without producing sedation is much wider than with reserpine. However, large doses (4.5 mg./kg.) of the drug elicit characteristic reserpinelike effects, including sedation with active closure of eyelids and decreased locomotor activity.

The effects of 50 μg./kg. of syrosingopine are not cumulative when the drug is given daily for 10 days; correspondingly no sedation and only a small decline in the content of brain amines are induced. In contrast, a single dose of 50 μg./kg. of reserpine depletes the content of brain norepinephrine and serotonin to about 60 per cent of normal; the same dose given daily for four days further depletes brain amines and produces progressively deeper sedation. Both drugs completely deplete heart norepinephrine with the first dose and maintain the depletion over the 10-day period.[8]

The cardiovascular effects of the chemical sympathectomy induced by syrosingopine were determined in dogs, injected intravenously with 0.5 mg./kg. of the drug. This dose depletes most of the heart norepinephrine, but does not affect brain amines nor induce overt sedation; in contrast, the same dose of reserpine elicits marked sedation. Syrosingopine liberates some serotonin from platelets and intestine, although much less than that liberated by reserpine.

The mean arterial pressure of the dogs (anesthetized with pentobarbital) falls gradually, and in about four hours averages 44 mm. Hg below that of the control group. In addition the mean heart rate is lowered by about 40 per cent. The pressure responses to carotid occlusion and to stimulation of the central end of the cut vagus is reduced by about 70 per cent. These effects were shown to be a result of the inactivation of the peripheral sympathetic system. Thus adrenalectomized animals do not show a pressor response to tetramethylammonium; rather they show a depressor response. Furthermore, the response to electrical stimulation of the celiac ganglion is reduced by about 65 per cent.

Another similarity between the effects of syrosingopine and of sympathectomy is the enhanced cardiovascular responses to administered norepinephrine, both in heart rate and in blood pressure. In fact norepinephrine increases the heart rate of drug-treated animals in doses that do not increase the heart rate in control animals. It may be concluded from these results that the cardiovascular effects of both syrosingopine and reserpine may be due to the loss of norepinephrine at peripheral nerve endings.[8] The question arises whether reserpine, like chlorpromazine, also depresses central sympathetic tone. Evidence supports the view that the action of reserpine on the sympathetic nervous system is a completely peripheral one. For example, tetrabenazine, a benzoquinolizine derivative having reserpinelike activity, releases brain serotonin and norepinephrine, but does not deplete the peripheral amines.[9] Correspondingly, the drug elicits central actions typical of reserpine, but does not appreciably lower blood pressure. Further support for the view that reserpine does not lower central sympathetic tone was obtained from the studies of Iggo and Vogt,[10] showing that large doses of reserpine do not lower the discharge of electric impulses into preganglionic sympathetic fibers. Instead of lowering central sympathetic output, reserpine and tetrabenazine (as well as syrosingopine in large doses) increase parasympathetic discharge from the central nervous system.

A main drawback to the use of reserpine in treatment of hypertension is the difficulty of maintaining a dosage schedule that lowers blood pressure without producing deep mental depression. Ideally the dosage should be sufficient to lower peripheral norepinephrine, but not the brain amines. Reserpine is readily absorbed but is rapidly destroyed in the intestine, due presumably to hydrolytic cleavage. For instance, the intravenous injection in rabbits of 4 mg./kg. of reserpine elicits a profound sedation lasting about three days, but the same dose given orally produces a barely perceptible sedation. When a patient is maintained on a certain daily dose of drug, it is presumed that the extent of its intestinal inactivation remains constant. Considering the cumulative action of reserpine and the narrow margin between the dosages eliciting hypotension and sedation, it is not surprising that serious central depression occurs in some patients on *Rauwolfia* therapy. Although syrosingopine is also unstable in the intestine, so that only a small part of the orally administered drug reaches the blood stream, the relatively selective action on peripheral norepinephrine stores should impart a greater margin of safety to this drug.

These results suggest certain criteria for a hypotensive agent that acts by producing chemical sympathectomy: the compound should act specifically at sympathetic nerve endings, it should be stable in the intestine, and it should be readily absorbed.

We now turn to two other drugs, guanethidine and bretylium, which also appear to produce chemical sympathectomy. Both drugs lower arterial blood pressure through a specific and prolonged inactivation of the peripheral sympathetic nervous system. Their effects cannot be attributed to a blocking of ganglionic transmission or to a blocking of the action of norepinephrine; instead the drugs appear to act on the postganglionic nerve fiber or at the nerve ending or between the nerve ending and the sympathetic neuromuscular junction.[11,12] Neither drug exerts an appreciable action on the central nervous system since each is highly ionized and does not readily cross the blood brain barrier.

Guanethidine

Our studies show that the injection of guanethidine into rabbits or cats lowers the norepinephrine content of heart, spleen, and intestine. The level of the amine in the heart declines over a period of four hours to about 15 per cent of normal, remains at this value for at least 18 hours, and then gradually rises, reaching the normal value in about seven days.[13] Guanethidine does not affect the content of catechol amine in the adrenal medulla. Of particular interest is the failure of the drug to lower the content of brain catechol amine. This is not surprising, however, since guanethidine does not penetrate the brain in appreciable amounts.

Although guanethidine produces chemical sympathectomy by depleting norepinephrine from peripheral nerve endings, the drug does not lower the serotin content of platelets, intestine, or brain. Accordingly, the compound satisfies certain criteria proposed for a compound that produces chemical sympathectomy: it is specific in that it selectively lowers the norepinephrine content at peripheral sites and does not affect serotonin stores; in addition, the compound is stable in the intestine. However, absorption of the drug is relatively slow due to its high degree of ionization and its low lipid solubility.

The question arises as to how guanethidine lowers the content of norepinephrine in peripheral tissues. It is probable that its mechanism differs from that of reserpine, since it lowers the level of heart norepinephrine more slowly and does not lower the level of peripheral serotonin. Work is now in progress to ascertain whether guanethidine lowers norepinephrine by releasing the amine or by blocking its synthesis.

Bretylium

Bretylium and guanethidine do not appear to act by the same mechanism. We have shown that the intravenous injection into rabbits of 12.5 mg./kg. of bretylium (as the tosylate salt) inactivates the peripheral sympathetic system, but does not lower the content of norepinephrine in the heart. It may be concluded that the drug does not act by depleting norepinephrine or by inhibiting its synthesis. It has been shown that stimulation of the splenic nerve fails to release norepinephrine in the presence of bretylium;[12] it is possible therefore that the drug causes a failure in the mechanism leading to release of norepinephrine at sympathetic nerve endings. It is also possible that the drug acts as a local anesthetic in the fine terminal endings of the postganglionic sympathetic nerves.[12]

It is of considerable interest that although bretylium prevents the release of norepinephrine by sympathetic nerve stimulation it does not prevent its release by reserpine.

Bretylium seems to be highly specific in that it appears to act only on the peripheral sympathetic nervous system. Since it is a quaternary ammonium compound, it is presumably stable in the intestine but, like other quaternary compounds, it is not readily absorbed.

Depletion of Norepinephrine at Sympathetic Ganglia

For some time it has been known that peripheral sympathetic ganglia contain considerable amounts of catechol amines that are released together with acetylcholine on preganglionic stimulation.[14] To gain some insight into the possible role of norepinephrine at sympathetic ganglia, S. Spector, in our laboratory, and E. Costa* have studied the conduction of nerve impulses across sympathetic ganglia after depletion of the amines by reserpine. On electrical stimulation of preganglionic nerves in cats, the potential evoked postganglionically is greatly enhanced. This suggests that norepinephrine in sympathetic ganglia may modulate the action of acetylcholine by counteracting its effect. This view is in accord with that suggested a number of years ago by Marrazzi.[15] Similar results have been obtained in animals treated with bretylium or with adrenergic blockade agents.

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It is possible that increasing the content of norepinephrine in ganglia may reduce the response of acetylcholine. Work is now in progress to see whether the hypotensive action of monoamine oxidase inhibitors may be explained in this way.

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HUMAN PHARMACOLOGY OF GUANETHIDINE

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Introduction

Although there is still lack of universal agreement that reduction in blood pressure will provide significant benefit to patients with hypertensive vascular disease, most clinicians feel that the availability of a drug that could lower arterial pressure to normal or nearly normal levels without producing intolerable side effects would be of outstanding clinical interest. Carefully controlled investigations of the hypotensive agents currently in widespread use, such as the "Veterans Administration Cooperative Study of Antihypertensive Drugs,"[1] have shown that reduction in blood pressure, which is at best quite moderate, can be achieved in hypertensive patients, an average decrease in diastolic pressure of 12 to 13 mm. Hg being obtainable with combinations of reserpine and hydralazine or reserpine and a ganglion-blocking drug. Further reduction in blood pressure has proved unobtainable because of side effects, the parasympatholytic side effects of the ganglion-blocking chemicals being particularly distressing. The recent availability of guanethidine ([2-(octahydro-1-azocinyl)ethyl]guanidine sulfate), a hypotensive agent that inhibits release of the chemical mediator from sympathetic nerve endings, has made possible the study of a drug that lowers blood pressure effectively in hypertensive patients without producing the parasympatholytic side effects of ganglionic blockade.[2-4]

Data from Animal Experiments

Maxwell[5] has shown that guanethidine produces prolonged blockade of the pressor response to electric stimulation of the great splanchnic nerve or the celiac ganglion in the dog, without preventing the hypertensive effect of infused *l*-norepinephrine. Guanethidine also prevents contraction of the nictitating membrane normally produced by electric stimulation of preganglionic cervical sympathetic fibers. Despite the inability of electric stimulation of preganglionic neurons to produce a normal effector response during the action of the drug, guanethidine did not prevent transmission of electric impulses along preganglionic sympathetic nerves, across sympathetic ganglia, or along postganglionic nerves. Thus, although the drug prevents the usual effects of stimulating sympathetic preganglionic efferent neurons, it does not interfere with electric transmission along nerves nor does it render smooth muscle incapable of contracting in response in circulating catecholamines. It is therefore assumed that guanethidine prevents release of the sympathetic neuroeffector chemical mediator from postganglionic sympathetic nerve terminals in response to nerve stimuli. Maxwell[5] also demonstrated that guanethidine administration is accompanied by decrease in the catecholamine content of aorta and heart in experimental animals.

The effects described above are slow in onset, reach a maximal degree in about

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48 hours, and last 7 to 10 days. In the first hour following intravenous administration of the drug, there was a brief moderate pressor response accompanied by mydriasis and piloerection. This early response could be blocked by pretreatment with phentolamine (Regitine).

In summary, guanethidine appears to discharge initially catecholamines from sympathetic nerve endings and subsequently to produce prolonged blockade of release of the neuroeffector mediator in response to nerve stimulation.

Effects of Guanethidine in Human Hypertension

Reduction in blood pressure. Studies done in our laboratory of 30 male patients hospitalized with severe hypertensive vascular disease, each of whom had diastolic pressure averaging more than 105 mm. Hg during a control period of at least six days in the hospital without any antihypertensive medications, have demonstrated marked reduction in blood pressure in response to treatment with guanethidine. Guanethidine was administered orally in doses of 150 or 200 mg. on the first day, one half the initial dose on the second day, and 25 to 75 mg. as single doses daily thereafter, the amount adjusted to achieve maximal reduction in blood pressure without intolerable side effects. The changes in blood pressure are depicted in FIGURE 1. Standing blood pressure was reduced more than was lying, and systolic pressure fell more than diastolic in either posture. Average reduction in standing diastolic pressure was from 126 to 87 mm. Hg, or 30 per cent. Fairly wide fluctuation in blood pressure was observed even during the height of the guanethidine effect, the lowest blood pressure generally being observed in the morning on arising, with a gradual increase of 10 to 20 mm. Hg during the day. Using the dosage schedule employed, maximal reduction in blood pressure was achieved in 48 to 72 hours. Following cessation of treatment, maximal reduction in blood pressure persisted for 3 or 4 days. Blood pressure then gradually returned to the pretreatment level in 7 to 21 days.

Of the 30 patients initially studied in the hospital, 15 who were able to record their own blood pressures twice daily at home have been continued on guanethidine treatment after discharge. In 13 of these, now observed for more than four months, successful reduction in blood pressure has continued in 11, while two have reported orthostatic dizziness and fainting so troublesome as to prevent any reduction in sitting blood pressure. A comparison of the averages of 60 individual recordings of diastolic pressure made by each of the 13 patients during the latest month of treatment, with their pretreatment pressures, is shown in FIGURE 2. For the group of 13 subjects there was an average reduction in diastolic pressure of 19 mm. Hg from a pretreatment average of 132 mm. Hg. Progressive increase in the dose of guanethidine required to maintain reduction in blood pressure was not noted.

Following intravenous administration, guanethidine, in doses approximating 0.5 mg./kg., has been shown by Imhof[6] and others to have an initial pressor effect, beginning 6 to 8 min. after administration of the drug, followed by a depressor response that began about an hour after administration, was maximum in 4 to 6 hours, and lasted 1 to 2 days. There was increase in pulse pressure during the pressor response and decrease in pulse pressure during the depressor phase. Although the pressor phase was seen in normal subjects and in hypertensive patients, the depressor phase tended to be more marked the higher the pretreatment blood pressure. The initial pressor phase was blocked by pretreatment with phentolamine, but the subsequent depressor phase was not. Imhof also demonstrated that, during the depressor phase of guanethidine action, patients are abnormally hyperresponsive to infused *l*-norepinephrine,

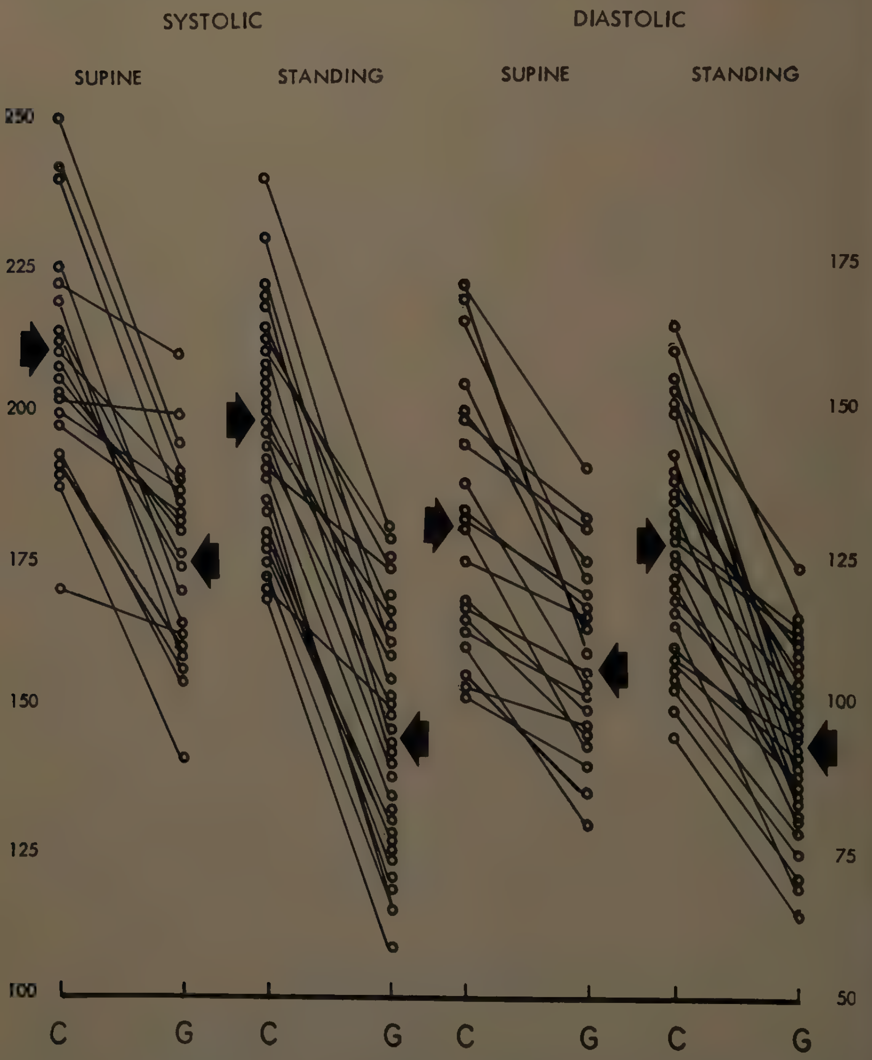

FIGURE 1. Reduction in blood pressure during guanethidine administration to 30 patients with hypertensive vascular disease. Each point in the control columns, labeled "C," is the average of 12 consecutive measurements recorded by nurses on the fourth, fifth, and sixth hospital days, prior to any therapy. Each point in the columns labeled "G" represents the average of 20 measurements by nurses on five consecutive days of maximal reduction in blood pressure associated with administration of guanethidine. Arrows denote the mean of each vertical column.

attaining much greater increases in blood pressure in response to standard infusions than did the same patients prior to guanethidine administration.

When patients had developed reduction in blood pressure following intravenous administration of guanethidine in the supine position, tilting of the

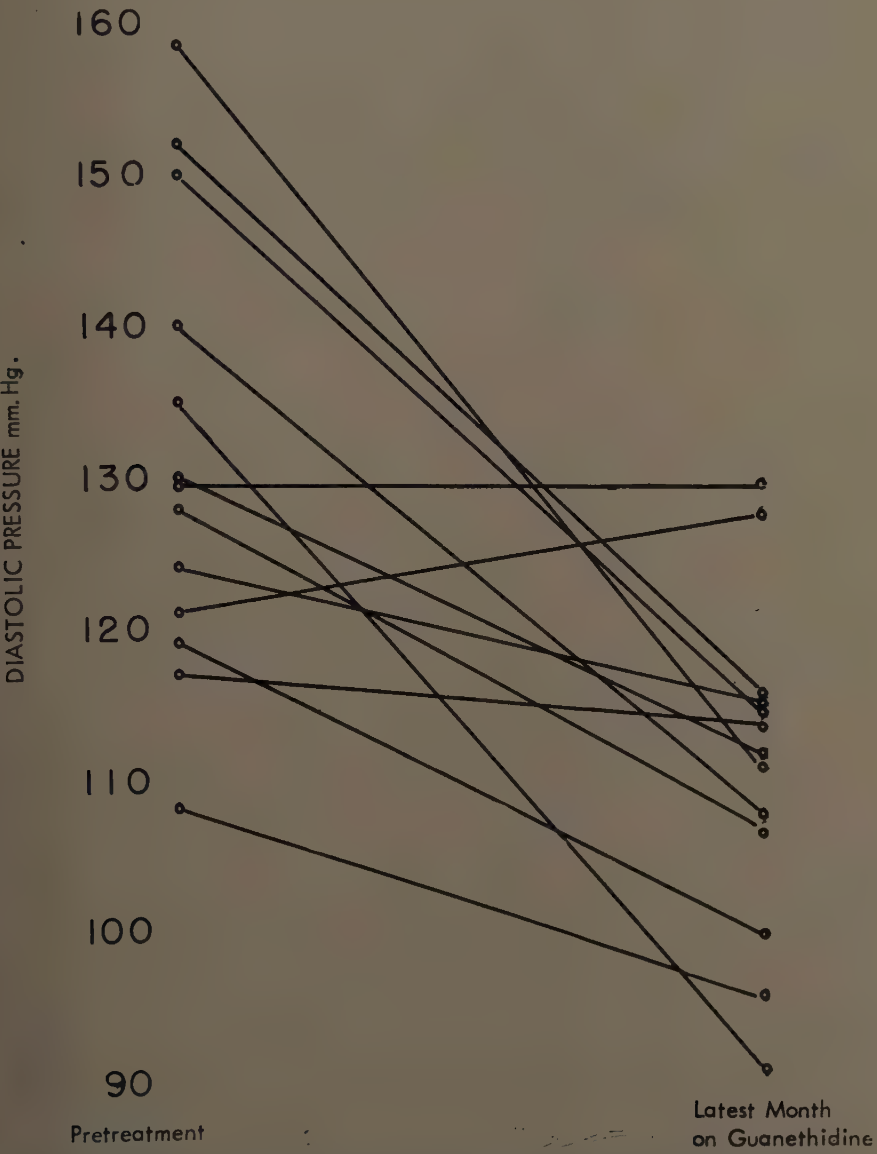

FIGURE 2. Reduction in blood pressure maintained in patients followed longer than four months. Each pretreatment point is the average of 12 measurements with the patient supine on the fourth, fifth, and sixth hospital days prior to antihypertensive therapy. Each point in the right column is the average of 60 pressures, recorded twice daily by the patient in the sitting position, during the last month of guanethidine administration.

table to 60° from horizontal with the head up and feet down resulted in marked further reduction in blood pressure and pulse pressure within 4 or 5 min.[6] Return of the table to the horizontal position was followed by a hypertensive "overshoot," with blood pressures considerably higher than before the tilting and considerably higher than the posttilting pressures observed in the same patients prior to guanethidine administration. The posttilt "overshoot" was blocked by administration of phentolamine just before tilting or during the early minutes after tilting; therefore, although it may have been due in part to return to the active circulation of blood pooled in the peripheral veins during quiet standing, it must also have been influenced considerably by catecholamines presumably released from the adrenal medulla under the stimulus of hypotension. Although no direct evidence regarding the effect of guanethidine on the adrenal medulla has been reported, this abolition of the posttilt overshoot by pretreatment with phentolamine hints that guanethidine does not interfere with release of *l*-norepinephrine from the adrenal.

TABLE 1

CIRCULATORY EFFECTS OF GUANETHIDINE*

	Control		During drug	
	Supine	Tilt 40°	Supine	Tilt 40°
Mean arterial pressure (mm. Hg)	(17) 157 ± 24	(23) 150 ± 24	(20) 126 ± 16†	(21) 99 ± 22†
Cardiac output (l./min.)	(21) 6.6 ± 1.7	(23) 5.5 ± 1.8	(20) 5.9 ± 1.7	(21) 4.4 ± 1.2†
Peripheral resistance (dyne-sec./$cm.^5$)	(21) 2144 ± 801	(23) 2450 ± 943	(20) 1846 ± 642	(21) 1875 ± 531†
Heart rate (beats/min.)	(21) 75	(23) 76	(20) 61	(21) 64
Stroke volume (cc./min.)	(21) 91	(23) 72	(20) 98	(21) 72

* Figures are mean ±1 standard deviation. In parentheses are the numbers of individual determinations from which corresponding means were calculated.

† Mean significantly different from control value in same position ($P < 0.05$).

Heart rate. When guanethidine is administered intravenously, there is an initial rise in heart rate accompanying the initial rise in blood pressure. As hypotension develops later in the course of action of guanethidine, gradual slowing of the heart ensues. In general, bradycardia parallels reduction in blood pressure, is most marked in the early morning, and rises somewhat as blood pressure rises during the course of the day. Heart rates less than 50 were not observed in our series.

Effects of guanethidine on cardiac output. TABLE 1 presents changes in cardiac output, total peripheral resistance, and associated measurements in a series of 10 hypertensive patients in whom duplicate determinations of cardiac output by the indicator-dilution method were made in both the supine and the 40° head-up tilted position, prior to administration of the drug. Duplicate determinations in each position were repeated about 4 to 10 days later, during the height of blood pressure reduction induced by orally administered guanethidine. FIGURE 3 shows the individual changes in cardiac output as-

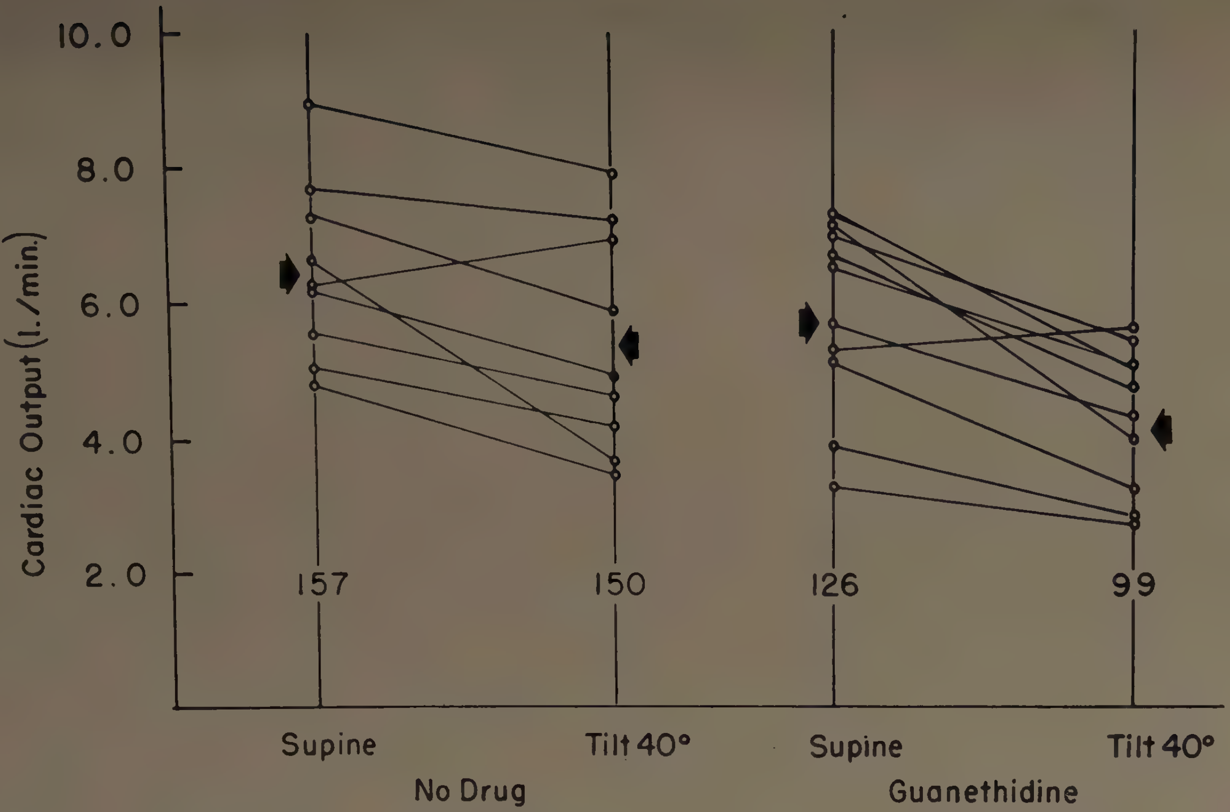

FIGURE 3. Effect of guanethidine on cardiac output. Each circle represents the average of 2 estimates of cardiac output, by the dye-dilution method, separated by 5 min. The numbers below each column are mean arterial pressures, the average of the group.

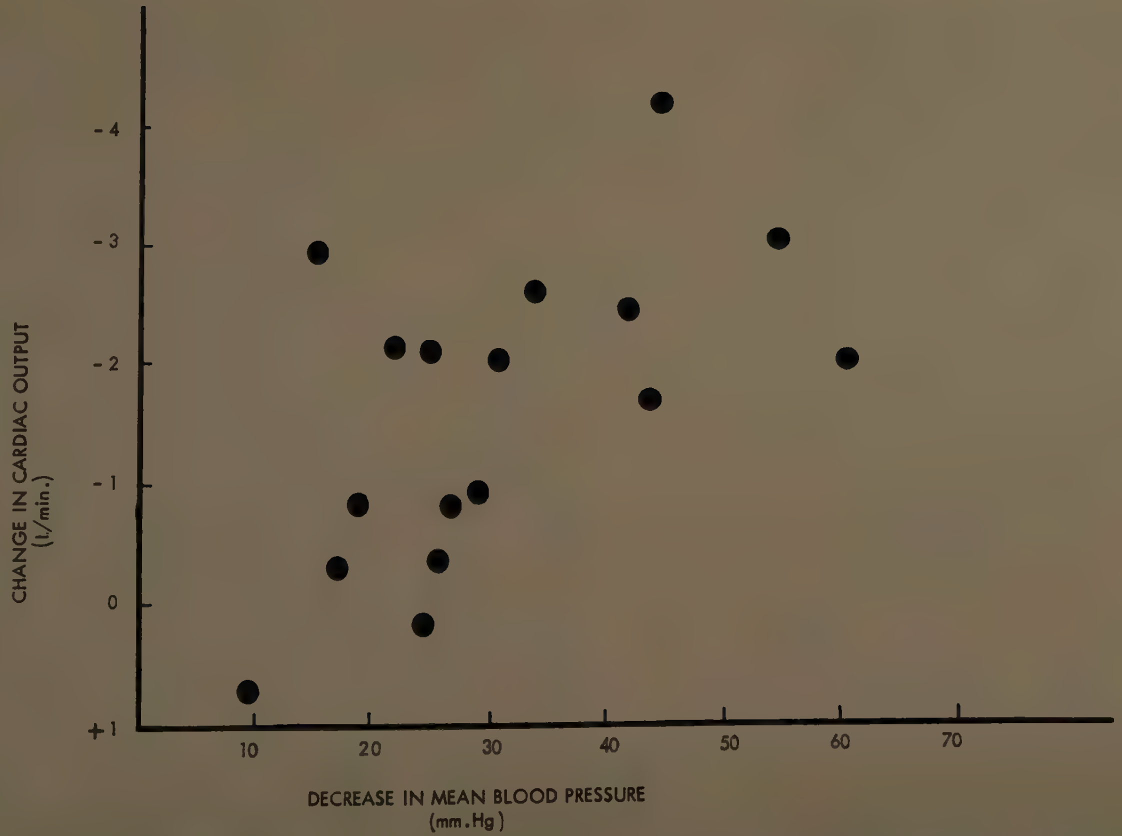

FIGURE 4. Correlation between reduction in blood pressure and in cardiac outputs associated with guanethidine treatment.

sociated with administration of the drug. It will be noted that reduction in cardiac output occurred in most subjects and was most marked in the 40°-tilted posture. FIGURE 4 shows that there was good correlation between the degree of reduction in blood pressure and the reduction in cardiac output. There was moderate reduction in peripheral resistance in the supine position, but the lack of change in vascular resistance during marked reduction in blood pressure associated with orthostasis shows that blood pressure can be lowered during guanethidine treatment without change in total peripheral resistance. In so far as calculated peripheral resistance may be assumed to represent changes in arteriolar caliber, this lack of marked change in resistance suggests that guanethidine does not primarily dilate arterioles. The orthostatic fainting induced by guanethidine also suggests that the drug inhibits sympathetic venoconstrictor impulses with dilation of peripheral veins, pooling of blood in the periphery, decline in venous return and, hence, in cardiac output and arterial pressure. This theory that the circulatory effects of guanethidine are secondary to inhibition of sympathetic venoconstriction is supported by the observation of Imhof,[6] that the orthostatic reduction in blood pressure induced by guanethidine is overcome by inflation of a "g-suit" to pressures that prevent the pooling of blood in veins in dependent portions of the body. To summarize, the reduction in cardiac output occurring with the standing position during guanethidine treatment is probably the result of such interference with sympathetic venoconstrictor mechanisms that there is pooling of blood in the peripheral venous circulation and reduction in venous return. The slighter reduction in cardiac output observed in the supine position is less easily explained. It is possible that guanethidine has effects on both arteriolar and venular constriction and that the latter effect is so prominent as to obscure the former during orthostasis.

The above-described effects on cardiac output are observed during the hypotensive phase of action of guanethidine. In the hour following intravenous injection of the drug there are rises in blood pressure and in pulse pressure, suggesting increase in stroke volume, changes that are consistent with the hypothesis that guanethidine results in release of catecholamines into the circulation during the early phases of its activity. Studies by Richardson,[7] using a strain gauge arch sewn to the right ventricle of dogs, have shown increase in the force of myocardial contraction during the early, hypertensive phase of action of guanethidine. Since heart rate, pulse pressure, and the force of myocardial contraction all increase during the early, hypertensive phase, it seems quite likely that cardiac output is increased during this period.

Effects of guanethidine on renal function. TABLE 2 shows the average results of treatment with guanethidine on glomerular filtration rate and renal plasma flow in 14 hypertensive subjects. FIGURE 5 shows individual changes in inulin clearance, used as a measure of glomerular filtration rate. Similar individual changes were noted in clearance of para-aminohippurate (PAH), used as a measure of renal plasma flow. Prior to treatment, glomerular filtration rate in these hypertensive patients was about 60 per cent of normal, and renal plasma flow was reduced even further, to 42 per cent of normal.

Administration of guanethidine was accompanied by reduction in glomerular filtration rate in 11 individuals, with slight rise in one and no change in two. Renal plasma flow fell in nine, rose in two, and was unchanged in three, the average of the group decreasing slightly. Blood pressure decreased proportionally more than did renal plasma flow during administration of the drug, so that there was slight decrease in calculated renal vascular resistance; however, this minimal improvement in vascular resistance seems clinically insignificant in the face of the prominent reduction in glomerular filtration rate, which decreased by 25 per cent. Clinically, blood urea nitrogen (BUN) values rose during treatment with guanethidine in about half the patients studied, but only when the pretreatment BUN was in excess of 25 mg./100 ml. The increases in BUN were of moderate magnitude, the largest change being from 46 to 78 mg./100 ml. In no case was it necessary to stop treatment with guanethidine because of oliguria or progressive azotemia. As judged from the BUN, renal function returned to pretreatment levels soon after the drug was stopped.

TABLE 2

EFFECTS OF GUANETHIDINE ON RENAL FUNCTION*

	Lying, no drug	Lying, guanethidine	Tilted, no drug	Tilted, guanethidine
Inulin clearance (ml./min./1.73 m.^{2})	67 ± 43	55 ± 35†	42 ± 28	31 ± 21†
PAH clearance (ml./min./1.73 m.^{2})	254 ± 158	230 ± 125	169 ± 121	140 ± 71†
Mean arterial pressure (mm. Hg)	158 ± 24	129 ± 16†	151 ± 24	109 ± 22†
Renal vascular resistance (mm. Hg/ml./min.)	0.82 ± 0.72	0.76 ± 0.69	1.15 ± 0.76	0.94 ± 0.61
Filtration fraction	0.27 ± 0.09	0.24 ± 0.05	0.31 ± 0.19	0.21 ± 0.09

* Figures are mean ±1 standard deviation.

† Means significantly different from values supine without drug ($P < 0.05$).

Guanethidine administration impairs the glomerular filtration rate, probably because the slight reduction in renal vascular resistance that accompanies the use of the drug is insufficient to maintain blood flow and filtration pressure during the marked reduction in blood pressure. Similar changes in renal function accompany the use of ganglion-blocking drugs[8] and the changes in renal function are probably related to reduction in blood pressure rather than to any specific harmful effect of guanethidine on the kidney. In three of the subjects studied, determinations of renal plasma flow and glomerular filtration rate during drug administration preceded the control observations, and in each of these, control measurements were larger than those made during guanethidine-induced reduction in blood pressure. This observation suggests that the drug has no residual effect on the kidney, once blood pressure has returned to pretreatment levels.

Brest[9] has shown a similar reduction in inulin and para-aminohippurate clearance about 1½ hours after intravenous injection of guanethidine, at the time of reduction of blood pressure. He also demonstrated decreased ex-

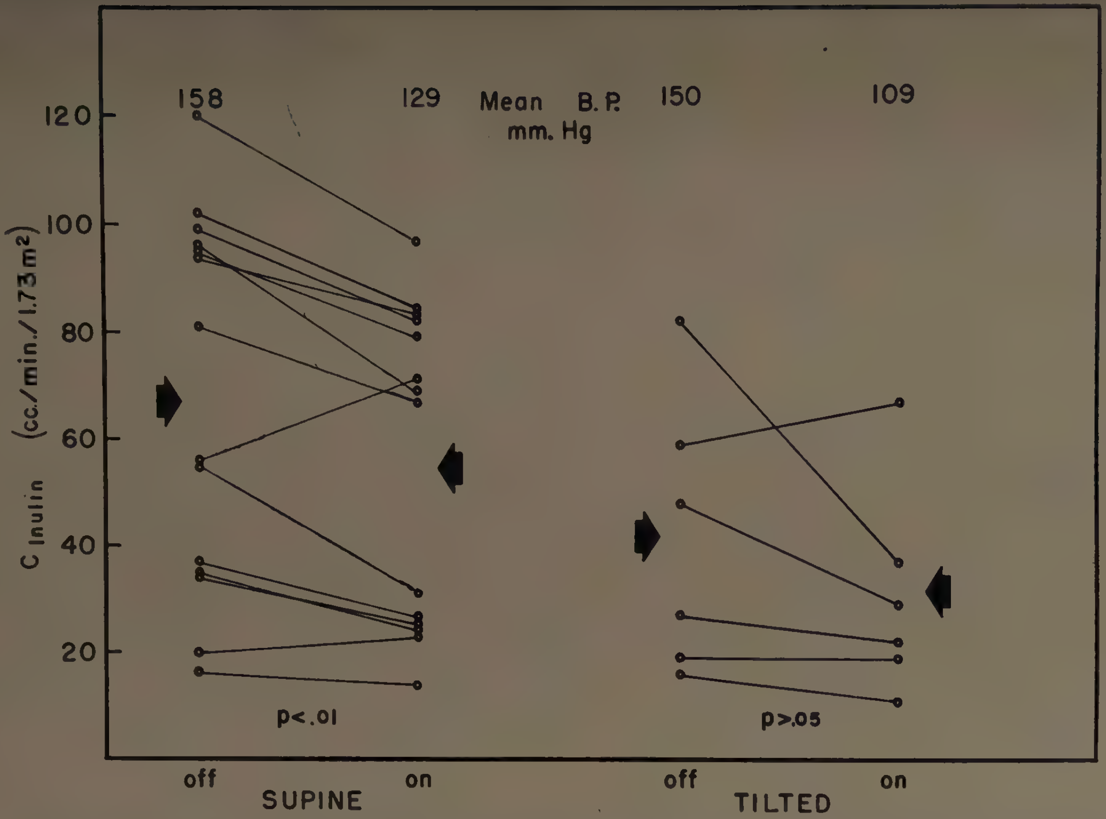

FIGURE 5. Change in glomerular filtration rate associated with guanethidine administration. Each point in the "off" columns represents the inulin clearance prior to therapy. Points in the "on" columns show clearances during maximal reduction in blood pressure accompanying guanethidine, 7 to 10 days later. During measurements shown in the "tilted" columns, patients were tilted about 40° from horizontal, with head up.

cretion of sodium, water, and potassium during the hypotensive phase of guanethidine administration.

Effects of guanethidine on other organs. The ophthalmic actions of guanethidine have been reported by Krishna,[10] who noted following intravenous administration of 0.25 to 0.5 mg./kg. to 20 normal subjects, slight miosis and definite decrease in intraocular pressure, the latter noticeable in 30 min. and lasting 8 hours. In 10 patients with glaucoma, all of whom had failed to respond to other medical therapy, moderate to marked reduction in intraocular pressure was observed in 5, with poor results in the other 5. Krishna thinks that the most likely explanation for the decrease in intraocular pressure is diminished rate of formation of aqueous humor.

The effects of guanethidine on other systems in the human body have not been reported. Information regarding the adrenal gland is strikingly lacking. Although the post-tilt overshoot in blood pressure observed in patients on guanethidine may be the result of increased adrenal release of catechol amines, no direct measurements of peripheral or adrenal vein catechol amine concentration during guanethidine administration have been reported.

Side Effects

Orthostatic hypotension is a common accompaniment of guanethidine administration. Dizziness on standing occurred in approximately one half of our patients, and fainting occurred in one sixth. Although this can hardly be classed as a side effect, postural dizziness is the symptom that most commonly prevents achievement of normal blood pressure, since supine blood pressures are usually definitely elevated even when standing blood pressures are normal or less than normal. Early morning orthostatic hypotension and dizziness are common during periods in which standing diastolic pressures rise to 100 or 110 mm. Hg during the remainder of the day.

Other untoward effects include diarrhea, three or four soft stools daily, which occurred in about a third of our patients and could be easily prevented with small doses of paregoric. Delayed ejaculation without difficulty in erection occurred in approximately 10 per cent. Ptosis, nausea, abdominal cramps, and bloating were uncommon accompaniments of treatment. Strikingly absent were the parasympatholytic effects of ganglion-blocking drugs. Weakness and lassitude, noted by other observers even in the absence of orthostatic hypotension, were not prominent complaints in our series. Repeated determinations of serum bilirubin, glutamic oxalacetic transaminase, CBC, and urinalysis showed no changes ascribable to guanethidine.

Summary

Guanethidine, a recently introduced antihypertensive agent, probably inhibits release of *l*-norepinephrine from sympathetic nerve endings. It does not block autonomic ganglia nor interfere with the parasympathetic nervous system. The hypotensive action of the drug is slow in onset, the maximal effect being noted 48 hours after the beginning of oral therapy. The agent has a prolonged effect, maximal reduction in blood pressure persisting 3 to 4 days after cessation of therapy. It has proved effective in reducing blood

pressure in each of 30 hypertensive patients treated for periods of up to 11 months. Reduction in cardiac output occurred during the decrease in blood pressure induced by guanethidine, suggesting that this drug does not primarily modify the abnormally increased arteriolar resistance that is the functional abnormality characteristic of hypertensive vascular disease. Reduction in renal blood flow and in glomerular filtration rate also accompanied use of the drug, but in no case did oliguria or progressive azotemia require that the drug be stopped. The agent slows heart rate and lowers standing blood pressures much more than supine blood pressures. When given intravenously, guanethidine has an initial pressor effect, probably related to immediate release of catecholamines from sympathetic nerve endings into the circulation. The drug provides hypotensive potency similar to that of ganglion-blocking agents with advantages of long duration of action and absence of parasympatholytic side effects. More extensive experience will be required to determine accurately its effectiveness in the control of hypertensive vascular disease.

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CLINICAL PHARMACOLOGY OF BRETYLIUM TOSYLATE: PRELIMINARY OBSERVATIONS

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The introduction of a new quaternary ammonium compound, bretylium tosylate,[1,2] which selectively blocks transmission in postganglionic sympathetic nerve fibers, may be an important advance in the treatment of hypertension and peripheral vascular diseases. Of equal interest is the opportunity it provides for the evaluation of the role of the sympathetic nervous system in the pathogenesis of these diseases.

An attempt has been made, therefore, to study the ability of bretylium to block sympathetically mediated reflexes in man, and to determine the changes it produces in the circulation. The effect on the blood pressure after parenteral and oral administration has also been assessed.

Methods

The effects of bretylium tosylate[2] have been studied in twenty patients (17 hypertensives and 3 normotensives). Injections were made in small quantities, approximately 12.5 mg., until a dose of 100 mg. was given over a 10-min. period. Measurements have been made of skin temperature (11 subjects), digital blood flow (9 subjects), forearm blood flow (13 subjects), and cardiac output (5 subjects). The skin temperature measurements were made with thermocouples applied to the dorsum of the hand and foot and, on some occasions, another on the trunk. Finger blood flow measurements were made with a conventional air-filled plethysmograph applied to the terminal phalanx, with venous occlusion applied to the same digit. The forearm flow was measured by a Whitney mercury-in-rubber strain gauge,[3] placed on the upper one third of the forearm, with venous occlusion applied by means of a sphygmomanometer cuff above the elbow. Another cuff at the wrist excluded the circulation from the hand. The room temperature in these studies varied from 72 to 76° F.

Cardiac output was measured by the indicator dilution method using indocyanine green. Injections were made through a polyethylene catheter inserted approximately 10 cm. centrally through a venipuncture in the antecubital fossa. The arterial dilution curve was recorded from the brachial artery by a Gilford† densitometer, which was calibrated with the known concentrations of dye in the patient's blood at the end of the procedure.

In 10 other patients, the effect of oral medication on the blood pressure was also determined. Blood pressure levels were determined by averaging readings taken four times daily in the hospital, or by measurements made twice daily by the subject himself at home.

Results

Characteristic effects of the drug. Intravenous injections of doses of 12.5 mg. of bretylium tosylate resulted in an immediate but short-lived respiratory stimulation. This was accompanied by vasoconstriction of the skin (FIGURE 1), which lasted 2 to 3 min. And sometimes a sharp elevation in blood pressure, of approximately 20/10 mm. Hg. followed. These changes recurred after each successive dose of the same magnitude. At the time of the blood pressure elevation, some degree of sympathetic blockade could be demonstrated by a fall in blood pressure on standing.

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† Gilford Instrument Company, Oberlin, Ohio.

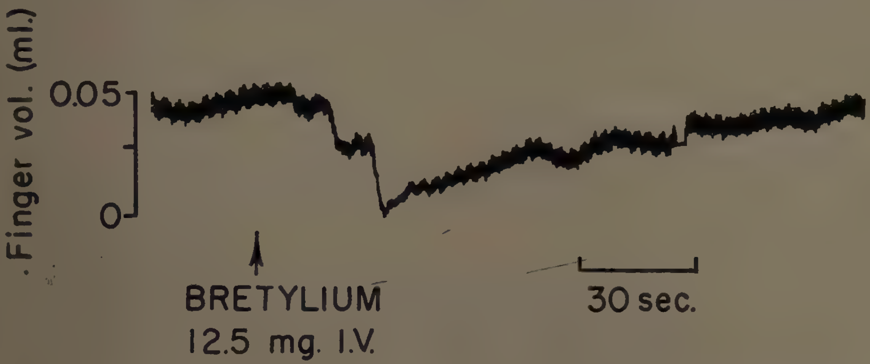

FIGURE 1. Digital plethysmogram showing the effect of an intravenous dose of bretylium.

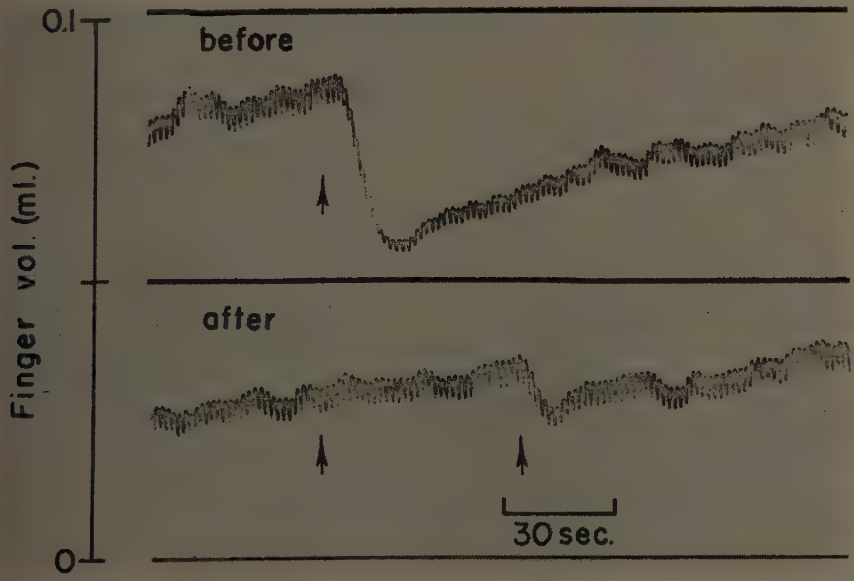

FIGURE 2. Effect of bretylium (100 mg. I.V.) on inspiratory reflex. The *arrow* indicates onset of deep inspiration.

In three patients a rise in blood pressure occurred some 6 to 9 hours after the administration of the drug. Two had received the drug intravenously and one orally. In view of the time that had elapsed, it is impossible to be certain of a causal relationship between the rise in pressure and the administration of the drug, but no other explanation could be found for the increase in pressure in any of the patients, and it exceeded the random variations in their blood pressure record. Reserpine (2.5 mg. I.M.) successfully reversed the rise in pressure.

The degree of blockade was assessed by eliciting several constrictive reflexes. The reflex most readily abolished was the vasoconstriction produced in the finger after a deep inspiration (FIGURE 2). A dose of 100 mg. intravenously prevented this reflex response in six of the eight subjects studied. Similarly, the overshoot produced by the Valsalva maneuver was abolished in two subjects (FIGURE 3). More potent reflexes were not completely suppressed. For example, the average rise in blood pressure produced by the standard cold pressor stimulus (FIGURE 3) was reduced from 55/38 to 30/18 mm. Hg.

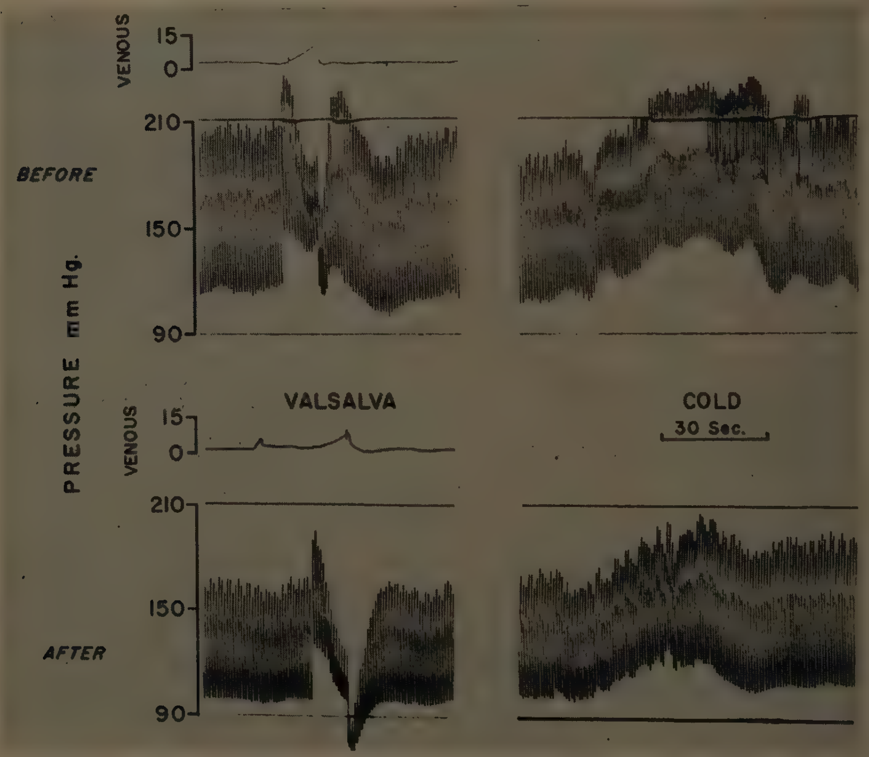

FIGURE 3. Effect of bretylium (100 mg. I.V.) on the Valsalva maneuver (*left*) and cold pressor test (*right*).

There were very few side effects produced by parenteral administration of bretylium; apart from the initial constrictive response, the only other effects were occasional flushing of the skin, nasal stuffiness, and injection of the conjunctivae. There were no alimentary or CNS effects.

Effects on the circulation. The most striking peripheral effect of bretylium was an increase in skin temperature of the hands and feet (FIGURE 4), which averaged 1.50° F. for the former and 2.5° F. for the latter. There was no change in temperature of the trunk. In association with this change there was an average increase of 35 per cent in finger blood flow. The forearm did not participate in this change. The average blood flow rate actually fell from 5.0 to 4.7 ml./100 ml./min.

The effects of bretylium on the circulation were compared with those of phentolamine in five subjects. Both drugs increased the pulse volume of the digit and usually abolished the response to a deep inspiration. In addition to this, phentolamine evoked an average increase in forearm flow from 5.3 to 6.3 ml./100 ml./min., and in one patient phentolamine increased cardiac output from 5.2 to 6.7 l./min., while bretylium produced little change.

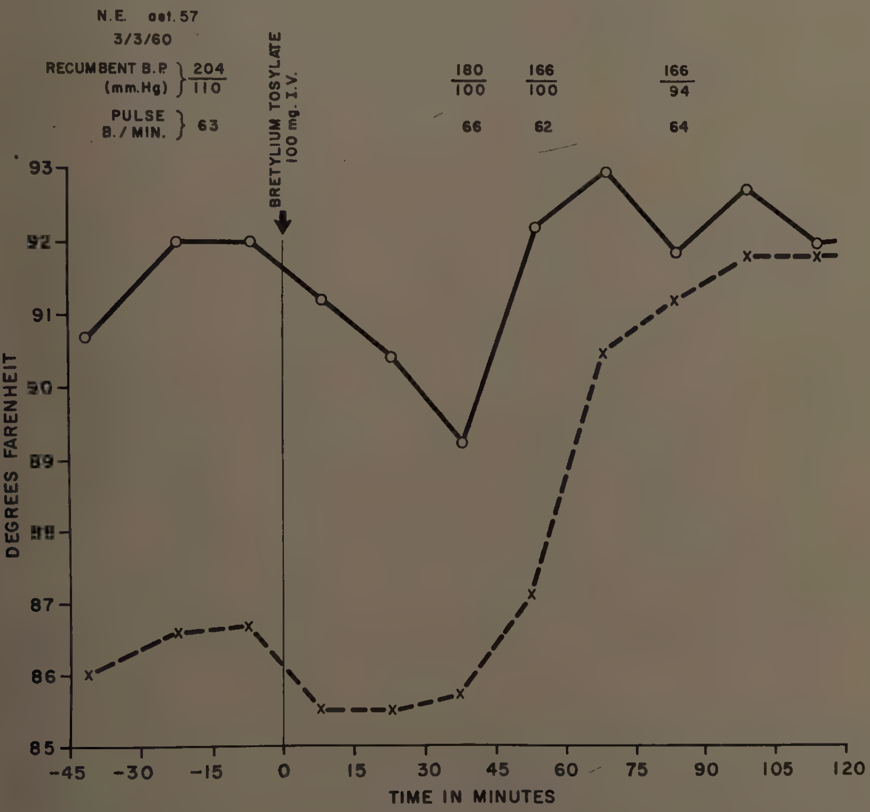

FIGURE 4. Effect of bretylium tosylate on hand (*o*) and foot (*x*) temperatures.

In the five patients in whom measurements of cardiac output were made there was a slight mean reduction from 5.2 to 4.9 l./min., at which time the mean blood pressure fell from 135 to 130 mm. Hg. Each patient showing a fall in blood pressure had a simultaneous reduction in output, with no change in calculated peripheral resistance.

Effect on the blood pressure. The administration of 100 mg. of bretylium tosylate intravenously to 17 hypertensive patients in the recumbent position resulted in a small fall in recumbent blood pressure, averaging 14/6 mm. Hg (TABLE 1). This was accompanied by a slight decrease in heart rate from 77 to 74 beats/min. Records of blood pressure taken after the hemodynamic studies were complete showed a small increase in hypotensive effect with time, the maximal response averaging 22/14 mm. Hg (TABLE 1). The standing blood pressure showed a much greater reduction, with an average of 35/19 mm. Hg. The diastolic fall is an estimate, since the response could not be recorded with accuracy in two patients. The average duration of effect of this dose of bretylium was 10 hours.

TABLE 1

THE EFFECT OF A SINGLE INTRAVENOUS DOSE (100 MG. I.V.) OF BRETYLIUM TOSYLATE ON THE BLOOD PRESSURE IN 17 HYPERTENSIVES

Acute effects (within 60 min.)		Later effects Maximum pressure change (mm. Hg)				
Initial recumbent pressure and change (mm. Hg)		Recumbent		Standing		Duration (hours)
Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	
170 (+4)	98 (0)	−10	−10	−15	−10	6
200 (−34)	110 (−16)	−45	−20	−52	−30+	8.5
172 (−12)	111 (−1)	−12	−12	−40	−20	18
198 (−8)	120 (0)	−8	0	−30	−5	3
235 (−10)	98 (−2)	—	—	—	—	—
150 (0)	100 (0)	0	0	−15	−5	6
185 (−16)	116 (−10)	−20	−10	−60	−26	6
220 (0)	130 (0)	−20	−15	−40	−15	11
195 (−14)	118 (−8)	−30	−15	−20	−30	8
220 (−10)	108 (−3)	−20	−10	−30	−30	12
205 (−81)	138 (−58)	−80	−50	—	—	10
230 (−38)	124 (−20)	−60	−34	−90	−11+	10
145 (−5)	100 (+10)	0	0	−18	−18	14
220 (−26)	120 (+6)	−30	−20	−40	−30	9
208 (+6)	110 (0)	−5	0	−5	−5	8
196 (+6)	116 (+8)	−10	−10	−40	−20	12
174 (0)	134 (−6)	−5	−10	−25	−20	16
Av. 196 (−14)	115 (−6)	−22	−14	−35	−19	10

Only four patients showed a fall in pressure of 10 mm. Hg or more in systolic and diastolic levels in the recumbent position, and in one of these the fall was 81/58 mm. Hg, reducing his pressure to 124/80 mm. Hg. This subject was also unusually sensitive to a ganglion-blocking agent. However when a second test with the same dose of bretylium was made some days later, the fall in pressure was only 12/8 mm. Hg, and the resulting level or "floor" of pressure was higher: 156/96 mm. Hg.

Effects of oral medication. In 10 patients, studies of the effect of oral administration of bretylium showed that the effective dose varied from 600 to 3200 mg./day. The average fall in pressure at optimum dosage was 11/13 mm. Hg in the recumbent position, and 32/22 mm. Hg in the standing position (TABLE 2).

The effect on the standing pressure was greater in the morning than in the evening. In addition to dizziness, presumably usually related to orthostatic hypotension, several patients noticed a sensation of extreme fatigue on arising, which passed off in the course of the morning. Tolerance to the drug was noticed in the first 2 to 3 weeks of medication, but this was not troublesome since individual titration of dosage was required. Other side effects have consisted of nasal stuffiness, injection of the conjunctivae, and vague abdominal discomfort. One patient had pain in the parotid gland on salivation.

Further studies to be reported elsewhere[4] have shown that the effect of bretylium on the blood pressure is very similar to that achieved by ganglion blockers. Some patients who respond to one type of drug, however, may be resistant to the other.

TABLE 2

THE EFFECT OF ORAL ADMINISTRATION OF BRETYLIUM TOSYLATE ON THE BLOOD PRESSURE

Patient	B. P. without (℞)		B. P. on bretylium tosylate			Duration (days)
	Lying (mm. Hg)	Standing (mm. Hg)	Final dose (mg./day)	Lying (mm. Hg)	Standing (mm. Hg)	
1	200/120	190/120	1500	200/110	155/100	5
2	145/100	145/100	1600	145/105	135/100	6
3	190/120	190/120	600	190/115	120/90	6
4*	200/140	170/130	800	160/120	120/90	9
5	210/130	200/125	600	190/105	160/90	13
6	220/150	190/120	1500	200/125	160/110	14
7	220/160	190/150	1100	186/133	167/132	30
8	186/120	164/128	800	188/122	137/95	30
9	170/110	160/100	900	191/100	163/90	60
10*	188/123	198/144	3200	174/108	181/125	75
Average	193/127	180/124	1260	182/114	148/102	25

* Two patients received chlorothiazide (1 gm./day) throughout the period of the test.

Conclusion

The initial vasoconstrictor effects of bretylium are almost certainly the result of local release of catecholamines, since they have been shown to occur after intra-arterial infusions of bretylium.[1] Lloyd Beck, in the Department of Pharmacology at the University of Michigan, has shown that the pressor response can be almost completely eliminated in dogs after reserpine has been used to deplete the peripheral stores of norepinephrine. The rise in pressure is also greatly enhanced by a ganglion-blocking drug. Furthermore, Beck has shown that the constrictive response may occur after the effect of direct sympathetic nerve stimulation has been blocked. This is an agreement with the clinical finding that postural hypotension may be elicited during the pressor response to the drug. It seems likely, therefore, that the release of norepinephrine is a peripheral effect occurring distally to the interruption of transmission in the sympathetic nerve fibers.

Bretylium, in the dose used in this study, was adequate to block some constrictive reflexes, but the response to the cold pressor test was not abolished. Since bretylium does not block the output from the adrenal medulla, it is possible that some sympatho-adrenal responses might remain even if the dose of the blocking agent were able to block neural transmission completely. The pattern of the changes in the peripheral circulation, manifested by an increase in flow to the hands and feet and little change in the forearm circulation, were similar to those observed with ganglion-blocking agents tetraethylammonium[5] and hexamethonium.[6,7] Apart from the initial vasoconstriction, bretylium did not appear to produce any effects that could not be attributed to blockade of sympathetic activity. For this reason it will be an invaluable tool in the study of the activity of the sympathetic nervous system in man, and will be of great value in assessing the activity of this system in hypertension.

In most recumbent hypertensive patients the fall in pressure caused by bretylium was negligible. Similarly, there was practically no change in heart rate. In those subjects in whom a fall in recumbent blood pressure occurred, a reduction in cardiac output was also observed. For the majority of hypertensives it seems unlikely that the sympathetic nervous system plays an important role in the etiology of hypertension. An occasional patient was seen in whom an unexpectedly large fall in pressure occurred; these patients will require further study.

The effect of oral medication, like that seen with parenteral administration, was mainly on the standing blood pressure. A small change was seen in the recumbent level, of magnitude similar to that seen after parenteral administration of the drug. The effective dose varied from 600 to 3200 mg./day. The drug produced a considerably greater effect on the blood on arising in the morning. The reason for this is unknown. Patients who have experienced low levels of pressure in the morning have either complained of dizziness and fainting, or of extreme lassitude. Since the blood pressure may fall to quite low levels without the presence of other warning side effects, this drug should be used with care in patients with cerebral or coronary artery disease.

In conclusion, bretylium provides a useful opportunity for the production of chemical sympathectomy in man which is symptomless if the patient remains in the recumbent position. On standing there is a profound fall in blood pressure. This action provides the basis for the use of bretylium in hypertension. Although the mode of action is nonphysiological and varies with posture throughout the day, it is, nevertheless, of great value in the treatment of patients with severe hypertension in whom simpler drugs, such as chlorothiazide and reserpine, have not effected an adequate reduction in pressure.

Summary

Bretylium tosylate in I.V. doses of 100 mg. produces blockade of some sympathetically mediated reflexes and a diminution of others. It results in an increase in blood flow to the hands and feet, but not to the forearm. The effect on the recumbent blood pressure is quite small, but marked postural hypotension always occurs.

Oral medication likewise produces its main effect on the standing pressure, and this is greater in the morning than evening levels.

Acknowledgment

I am indebted to Stanley T. Bloomfield, of Burroughs Wellcome Company, Tuckahoe, N. Y., for the supplies of bretylium tosylate (Darenthin) used in this investigation.

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THE EFFECT OF CHLOROTHIAZIDE AND ITS CONGENERS ON THE DIGITAL CIRCULATION IN NORMOTENSIVE SUBJECTS AND IN PATIENTS WITH ESSENTIAL HYPERTENSION

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The action of chlorothiazide or its congeners on the circulation is not clearly understood. It is known, for example, that these drugs can reduce the blood pressure of patients with essential hypertension and yet have no effect on the blood pressure of normal subjects,[1-4] and also that they increase the antihypertensive effect of other drugs such as the ganglion blockers.[5-7] Chlorothiazide decreases the plasma volume[8] and the cardiac output[9] of patients with hypertension; later, when plasma volume and cardiac output return to normal, blood pressure is still kept low by the drug.[10] It has also been shown that pressor response to injected *l*-norepinephrine (NE) is decreased in normotensive[11] as well as in hypertensive[12,13] subjects by chlorothiazide. The results, however, are not always clear-cut and there is much overlapping. Most workers agree that the circulatory effects are secondary to the direct action of chlorothiazide on the kidney, with resultant loss of sodium and potassium chloride and water,[1, 5,14] whereas others believe that the drug may have some additional direct action on the tissues and systemic blood vessels.[2] In order to clarify some of these questions, a study was undertaken in both normotensive and hypertensive subjects of the effect of these drugs on the digital circulation. Several factors could thus be studied concomitantly by established methods.[15-17]

Studies were completed on nine normotensive and ten hypertensive subjects before and after the administration of chlorothiazide at a dosage of 500 mg. twice daily for two weeks. Similar studies were carried out in four normotensive and four hypertensive subjects on hydrochlorothiazide (50 mg. twice daily for two weeks), and in three normotensive and three hypertensive subjects on benzydroflumethiazide (5 mg. twice daily for two weeks). At each session, brachial and digital blood pressures and digital blood flow were measured in three phases: (1) in the resting state under standardized conditions, including maintenance of room temperature between 26° and 29° C. (phase B); (2) after vasodilatation produced by indirect heating with a cradle baker over the trunk until positive heat balance was manifested by profuse diaphoresis, followed by the intravenous administration of 0.8 mg./kg. of SC 1950 (2,6-dimethyl-1,1-diethyl piperidinium bromide), a ganglion-blocking drug (phase A); and (3) with the conditions in phase A remaining constant during the intravenous infusion of NE and additional SC 1950 at a rate sufficient to bring the subject's blood pressure to its original value or somewhat higher (phase C). The in-

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fusion fluid contained 50 mg./cc. of glucose, 0.0122 mg./cc. of *l*-norepinephrine bitartrate and 0.09 mg./cc. of SC 1950, and the rate of its administration was regulated with an infusion pump.

Studies were not performed until the blood pressure level was stable. There were no untoward effects from this procedure except for occasional headache or chest pain associated with an excessive rise in blood pressure. Slowing the infusion rate was all that was necessary to decrease the blood pressure and eliminate these symptoms. In a few cases the studies were not completed in the resting state (phase B).

Flow in the digit was measured calorimetrically and both systolic and diastolic digital arterial pressures were measured with a Gaertner capsule. These pressure data were converted to mean pressure by adding one third of the pulse pressure to the diastolic value. A calculated venous pressure correction was subtracted from this, and the radius equivalent of the digital circulation was computed from flow and effective mean pressure by using Poiseuille's law. A calculated length factor was considered to be constant for the digital circulation, correction being made for variation in fingertip size. Correction was also made for critical closing pressure and/or apparent blood viscosity change in the constricted phases of the procedure. The radius equivalent of the digital circulation was calculated for the constricted as well as for the dilated state. From the digital blood pressures and the change in the radius equivalent, as measured during the two sets of experimental conditions, the work of vasoconstriction was calculated and, based upon the NE infusion rate, this value could be expressed as the work per milligram of infused NE per minute. The formula used for calculating work of vasoconstriction is:

$$w = 197P_1(r_1^2 - r_2^2) - \frac{16.1P_1^2}{Q_1}(r_1^6 - r_2^6)$$

in which w is work in ergs, P_1 is effective mean pressure, Q_1 is blood flow, r_1 is radius equivalent during vasodilatation, and r_2 is radius equivalent during vasoconstriction. The reliability and reproducibility of these results in individual subjects in normotensive and hypertensive groups were amply demonstrated.[15-17] Moderate variation in the rate of NE infusion did not modify appreciably the values for work of vasoconstriction per milligram of NE infused per minute.

Results

The results (TABLES 1 through 6) are complex and are best analyzed in some respects by considering the cases individually. It is apparent that the brachial as well as the digital blood pressures were reduced by all the drugs used in the hypertensive but not in the normotensive subjects. Another fairly consistent feature was the reduction of reactivity to NE in the hypertensive subjects by the three drugs. In normotensive subjects, on the other hand, the drugs produced either no change or an increase in reactivity to NE.

The other results were all more variable. Digital blood flow in both groups was either decreased, increased, or remained unchanged. Intrinsic digital vascular caliber (radius equivalent in the vasodilated state) was also either in-

TABLE 1

BEFORE (1) AND AFTER (2) 1000 MG. OF CHLOROTHIAZIDE DAILY FOR TWO WEEKS IN NINE NORMOTENSIVE SUBJECTS

A = after vasodilatation, B = before vasodilatation, C = after vasodilatation and NE infusion

Pt.	Age and sex	Phase	Brach. B.P. (mm. Hg)	Digital B.P. (mm. Hg)	Eff. mean dig. B.P. (mm. Hg)	Dig. blood flow (cc./cpr.^{2}skin/min.)	Radius equivalent (cm. $\times 10^{-2}$)	Work of vasoconstriction (10^3 ergs)	Rate of NE infusion (10^{-2}mg./min.)	Work/mg./min. (10^3 ergs/mg./min.)	Per cent change
1	32M	1A	114/76	94/62	60	0.31	3.1				
		1B	130/80	110/64	70	0.21	2.9	1.0			
		1C	170/102	152/94	99	0.35	2.9	1.0	1.44	72	
		2A	104/70	94/55	58	0.23	2.9				
		2B	120/80	104/64	68	0.21	2.8	0.45			
		2C	156/98	132/77	85	0.24	2.8	0.45	1.55	29	−61
2	20M	1A	132/76	106/66	64	0.37	3.2				
		1B	140/78	130/66	78	0.23	3.0	1.1			
		1C	160/90	150/84	90	0.38	3.1	0.54	1.5	37	
		2A	106/70	102/58	58	0.37	3.3				
		2B	136/70	130/60	72	0.27	3.1	1.0			
		2C	140/80	138/70	80	0.32	3.1	1.0	2.8	37	0
3	21M	1A	110/70	104/56	59	0.31	3.1				
		1B	124/70	108/60	63	0.31	3.1	0			
		1C	140/110	132/94	95	0.30	2.9	1.0	1.5	69	
		2A	120/80	109/61	63	0.32	3.2				
		2B	120/76	115/61	67	0.28	3.1	0.42			
		2C	196/106	172/90	102	0.35	3.0	0.89	0.83	110	+59
4	34M	1A	106/60	100/54	52	0.40	3.4				
		1B	126/76	118/68	72	0.32	3.2	1.0			
		1C	130/80	120/72	72	0.38	3.3	0.45	0.92	49	
		2A	106/50	88/50	52	0.28	3.1				
		2B	116/50	98/42	50	0.27	3.1	0			
		2C	140/86	114/74	75	0.30	3.0	0.27	0.87	31	−37
5	34F	1A	84/56	76/50	48	0.27	3.2				
		1B	96/66	87/58	60	0.19	3.0	0.83			
		1C	120/80	92/70	67	0.25	3.0	0.83	1.4	60	
		2A	80/66	70/54	46	0.30	3.3				
		2B	90/64	75/54	53	0.14	3.0	1.3			
		2C	110/76	100/66	67	0.25	3.0	1.3	1.3	95	+58
6	20M	1A	104/64	96/46	53	0.24	3.0				
		1B	120/70	114/64	71	0.23	2.9	0.43			
		1C	130/80	126/58	71	0.25	2.9	0.43	0.87	50	
		2A	110/70	87/45	44	0.35	3.5				
		2B	116/70	110/62	64	0.32	3.2	1.3			
		2C	130/86	130/60	69	0.33	3.2	1.3	1.4	92	+84
7	23M	1A	98/62	88/50	54	0.23	3.0				
		1B	110/70	96/60	63	0.22	2.9	0.40			
		1C	130/84	120/70	78	0.22	2.9	0.40	1.0	40	
		2A	104/68	90/52	58	0.18	2.7				
		2B	114/70	90/60	63	0.18	2.7	0			
		2C	134/88	118/72	79	0.19	2.6	0.44	0.91	48	+20

TABLE 1—*Continued*

Pt.	Age and sex	Phase	Brach. B.P. (mm. Hg)	Digital B.P. (mm. Hg)	Eff. mean dig. B.P. (mm. Hg)	Dig. blood flow (cc./cpr.^{2}skin/min.)	Radius equivalent (cm. × 10^{-2})	Work of vasoconstriction (10^3 ergs)	Rate of NE infusion (10^{-2}mg./min.)	Work/mg./min. (10^3 ergs/mg./min.)	Per cent change
8	29F	1A	96/60	88/52	52	0.25	3.1				
		1B	120/80	102/72	75	0.16	2.7	1.7			
		1C	130/84	106/68	69	0.28	3.0	0.19	0.84	23	
		2A	90/58	76/50	47	0.28	3.2				
		2B	104/78	98/70	67	0.29	3.1	0.41			
		2C	116/80	106/72	73	0.25	3.0	0.84	1.5	56	+143
9	23M	1A	114/70	98/56	58	0.30	3.1				
		1B	134/78	122/70	76	0.26	2.9	1.0			
		1C	154/98	142/80	88	0.32	2.9	1.0	1.5	69	
		2A	116/72	102/70	68	0.33	3.1				
		2B	130/72	116/62	68	0.28	3.0	0.51			
		2C	134/84	118/78	81	0.25	2.9	1.1	1.4	76	+10

creased, decreased, or remained unchanged in both groups. There was some correlation between a decrease or increase in the work of digital vasoconstriction in the resting state and the change in vascular reactivity after drug administration, but this relationship was by no means always consistent. Furthermore, the degree of change both in the normotensive and the hypertensive group was greater than the expected change attributable to chance between two tests in any given subject.[15-17]

There are at least four separate factors capable of influencing the digital blood pressure. One is a change in cardiac output that could in turn be influenced by a change in plasma volume. This would be reflected best by the digital blood flow after vasodilatation. The second is a change in the intrinsic caliber of the blood vessels (nonneurogenic), as influenced, for example, by the imbibition of or loss of edema fluid from the blood vessel wall.[18] This would be reflected best in the digit by change in the vasodilatation radius equivalent. A third factor is the degree of neurogenic vasoconstriction that in turn is influenced by the rate and intensity of sympathetic nerve discharge and the reactivity of the blood vessels to such discharge. The work of vasoconstriction in the resting state is most representative in the digit of the degree of neurogenic vasoconstriction. If the change is concordant with a change in NE reactivity, the latter factor is probably responsible for the change in work, whereas if it is discordant, one could assume that an increase in work is caused by increased sympathetic neural discharge or perhaps even by increased circulating NE.

It is possible to analyze each case in the hypertensive group with reference to these factors and to show that a different combination of factors is responsible for the decrease in the blood pressure in any given case. For example, in patient 12 the two factors responsible for the decrease in resting blood pressure were a decrease in NE reactivity, with a concordant decrease in resting work of vasoconstriction, together with a decrease in intrinsic blood flow. In pa-

TABLE 2

BEFORE (1) AND AFTER (2) 1000 MG. OF CHLOROTHIAZIDE DAILY FOR TWO WEEKS IN TEN HYPERTENSIVE SUBJECTS

A = after vasodilatation, B = before vasodilatation, C = after vasodilatation and NE infusion

Pt.	Age and sex	Phase	Brach. B.P. (mm. Hg)	Digital B.P. (mm. Hg)	Eff. mean dig. B.P. (mm. Hg)	Dig. blood flow (cc./cpr.²skin/min.)	Radius equivalent (cm. × 10⁻²)	Work of vasoconstriction (10³ ergs)	Rate of NE infusion (10⁻²mg./min.)	Work/mg./min. (10³ ergs/mg./min.)	Per cent change
10	50F	1A	230/126	181/71	95	0.25	2.8				
		1B	236/130	160/70	97	0.14	2.5	2.3			
		1C	250/126	187/71	102	0.19	2.6	1.4	0.84	167	
		2A	100/70	92/58	58	0.27	3.0				
		2B	140/90								
		2C	180/104	154/100	111	0.17	2.6	2.1	1.2	174	+4
11	51M	1A	150/106	149/66	84	0.24	2.7				
		1B	170/110								
		1C	174/114	152/106	110	0.27	2.6	0.58	0.9	66	
		2A	140/100	122/94	93	0.27	2.7				
		2B	156/100								
		2C	186/114	172/106	151	0.27	2.6	0.70	1.1	66	0
12	42F	1A	146/96	144/84	93	0.27	2.7				
		1B	190/110	178/92	119	0.04	2.1	4.6			
		1C	210/130	197/122	138	0.21	2.4	2.1	1.1	192	
		2A	110/80	116/70	77	0.21	2.7				
		2B	144/92	128/80	89	0.18	2.6	0.51			
		2C	180/110	170/102	118	0.18	2.5	1.1	1.0	103	−46
13	40F	1A	160/110	164/109	121	0.25	2.5				
		1B	230/140								
		1C	250/140	233/136	158	0.24	2.4	0.77	0.92	84	
		2A	182/98	172/94	108	0.28	2.6				
		2B	200/126								
		2C	220/130	196/114	131	0.23	2.5	0.77	0.93	83	−1
14	59M	1A	110/76	85/60	60	0.21	2.8				
		1B	150/86	123/79	90	0.11	2.4	2.0			
		1C	184/96	166/90	108	0.16	2.4	2.0	0.86	234	
		2A	120/74	97/56	56	0.34	3.2				
		2B	140/80	118/78	80	0.27	3.0	1.0			
		2C	160/90	140/88	93	0.28	2.9	1.6	0.88	180	−23
15	37F	1A	140/94	136/86	88	0.36	2.9				
		1B	164/110	143/108	118	0.06	2.2	5.6			
		1C	210/126	198/114	126	0.32	2.7	1.4	0.50	288	
		2A	108/76	94/72	70	0.22	2.7				
		2B	120/80	106/74	84	0.04	2.2	3.0			
		2C	150/104	152/94	105	0.19	2.5	1.1	0.97	115	−60
16	46F	1A	144/94	128/90	93	0.24	2.6				
		1B	180/110	172/100	120	0.10	2.2	2.9			
		1C	210/124	197/102	127	0.20	2.4	1.4	0.87	156	
		2A	126/80	120/64	73	0.25	2.8				
		2B	140/90	130/72	85	0.14	2.6	1.1			
		2C	180/110	168/88	103	0.28	2.7	0.54	0.86	63	−60

TABLE 2—*Continued*

Pt.	Age and sex	Phase	Brach. B.P. (mm. Hg)	Digital B.P. (mm. Hg)	Eff. mean dig. B.P. (mm. Hg)	Dig. blood flow (cc./cpr.²skin/min.)	Radius equivalent (cm. × 10⁻²)	Work of vasoconstriction (10³ ergs)	Rate of NE infusion (10⁻² mg./min.)	Work/mg./min. (10³ ergs/mg./min.)	Per cent change
17	47F	1A	150/82	142/64	78	0.31	2.9				
		1B	170/90	162/78	100	0.15	2.5	2.7			
		1C	190/104	164/94	103	0.35	2.8	0.60	0.53	114	
		2A	100/70	86/62	61	0.23	2.9				
		2B	154/84	145/77	98	0.06	2.1	4.3			
		2C	160/100	150/90	100	0.25	2.7	0.94	1.4	67	−41
18	59F	1A	140/60	132/62	77	0.20	2.7				
		1B	220/110	204/94	129	0.04	1.9	9.2			
		1C	210/108	202/100	125	0.22	2.5	0.94	0.92	103	
		2A	144/60	138/52	70	0.26	2.8				
		2B	180/86	168/80	104	0.11	2.4	2.4			
		2C	200/100	176/94	109	0.29	2.7	0.55	0.52	105	+2
19	49F	1A	126/76	112/72	74	0.29	2.9				
		1B	150/80	132/80	90	0.16	2.6	1.2			
		1C	176/100	140/96	101	0.24	2.7	1.1	1.6	74	
		2A	104/66	90/51	58	0.18	2.7				
		2B	124/70	106/64	71	0.16	2.6	0.45			
		2C	150/90	136/80	93	0.15	2.5	0.91	2.5	36	−51

tient 14, on the other hand, the factors relative to vasoconstrictive work were the same as in patient 12, but there was an increase in intrinsic blood flow, balanced by an increase in intrinsic vascular caliber. In patient 17 the relationship between the change in resting work and NE reactivity was discordant, and there was an increase in resting work. This was overbalanced, however, by a decrease in intrinsic flow that was responsible for the moderate decrease in blood pressure. In patient 18 the decrease in blood pressure was due almost entirely to a decrease in sympathetic nerve discharge, as manifested by a decrease in resting work of vasoconstriction. There are several patients (25, 27, 31) in the hypertensive group with low intrinsic blood flow, indicating severe arteriosclerotic involvement. Their patterns of change, however, did not differ significantly from those of the other hypertensive subjects.

On occasion, in the normotensive subjects, no significant effect whatsoever was produced on the circulation by the drug (patient 2). In patient 1, on the other hand, there was a decrease in NE reactivity with a concordant decrease in resting work, balanced by a decrease in intrinsic vascular caliber. It must be remembered that even small changes in caliber are potent, since they must be taken to the fourth power to be proportional to flow or pressure changes. In patient 4 the concordant decrease in resting work and NE reactivity and in intrinsic flow is balanced by a decrease in intrinsic vascular caliber. In patient 6 the concordant increase in NE reactivity and resting work and in intrinsic flow was balanced by an increased intrinsic vascular caliber. In patient 7, however, a decrease in resting work not associated with any change in NE reactivity but influenced also by a decrease in intrinsic flow, was balanced by a decrease in intrinsic vascular caliber. The relationship between resting work and NE reactivity was often discordant in these cases, but it was sometimes concordant. A slightly different pattern is presented by patient 23, where a concordant increase in resting work and NE reactivity and a decrease in intrinsic caliber were all balanced by a decrease in intrinsic flow. In patient 28, on the other hand, no great change occurred in resting work or reactivity, but an increase in intrinsic caliber was balanced by an increase in intrinsic flow. In other words, the failure of these drugs to affect blood pressure in the normotensive subject does not necessarily signify the absence of a vascular effect, but rather the balancing of effects acting in divergent directions, some of which perhaps are compensatory.

TABLE 3

BEFORE (1) AND AFTER (2) 100 MG. OF HYDROCHLOROTHIAZIDE DAILY FOR TWO WEEKS IN FOUR NORMOTENSIVE SUBJECTS

A = after vasodilatation, B = before vasodilatation, C = after vasodilatation and NE infusion

Pt.	Age and sex	Phase	Brach. B.P. (mm. Hg)	Digital B.P. (mm. Hg)	Eff. mean dig. B.P. (mm. Hg)	Dig. blood flow (cc./cpr.²skin/min.)	Radius equivalent (cm. × 10⁻²)	Work of vasoconstriction (10³ ergs)	Rate of NE infusion (10⁻²mg./min.)	Work/mg./min. (10³ ergs/mg./min.)	Per cent change
20	19M	1A	90/56	82/50	44	0.28	3.2				
		1B	100/66	94/58	67	0.08	2.6	2.8			
		1C	170/100	148/90	96	0.32	2.9	1.3	1.6	81	
		2A	100/66	86/48	47	0.30	3.3				
		2B	100/70	92/56	68	0	0	11.1			
		2C	126/84	112/78	78	0.28	3.0	1.3	0.88	150	+85
21	35M	1A	100/64	90/58	55	0.33	3.2				
		1B	120/70	98/62	60	0.33	3.2				
		1C	136/84	128/78	83	0.29	3.0	1.0	2.5	40	
		2A	104/64	88/58	55	0.32	3.2				
		2B	110/70	92/66	63	0.29	3.1	0.46			
		2C	134/84	122/80	83	0.26	2.9	1.5	1.5	102	+155
22	26F	1A	106/60	88/50	48	0.35	3.4				
		1B	124/76	98/64	67	0.19	3.0	1.9			
		1C	136/86	132/74	70	0.40	3.2	0.80	1.6	50	
		2A	94/64	96/64	62	0.28	3.0				
		2B	110/70	108/66	70	0.20	2.8	0.34			
		2C	120/70	116/64	71	0.27	2.9	0.52	0.77	66	+32
23	17M	1A	110/68	102/58	61	0.34	3.1				
		1B	116/70	108/60	68	0.31	3.0	0.39			
		1C	140/90	128/72	77	0.30	3.0	0.39	0.82	48	
		2A	100/62	116/64	72	0.23	2.8				
		2B	120/76	108/58	69	0.13	2.6	1.2			
		2C	138/100	134/88	75	0.21	2.6	1.2	0.84	140	+191

Discussion

It is clear that the most consistent change produced by these drugs in the hypertensive subject was a decrease in blood pressure associated with a decrease in NE reactivity. This probably does not represent a direct action of the drugs, since the effect is the opposite on NE reactivity in normotensive subjects. It is more likely, therefore, that the drug is acting by virtue of its major effect, that of sodium depletion. These experiments, in accord with those of other workers,[19,20] therefore implicate the sodium ion in the process of contractility of the smooth muscle of blood vessels. If the sodium ion acts directly, an optimum concentration could be postulated, both above and below which increased contractility is produced. If an enzyme system[21] is hypothesized to be involved, on the other hand, the sodium ion in normal concentration would

TABLE 4

BEFORE (1) AND AFTER (2) 100 MG. OF HYDROCHLOROTHIAZIDE DAILY FOR TWO WEEKS IN FOUR HYPERTENSIVE SUBJECTS

A = after vasodilatation, B = before vasodilatation, C = after vasodilatation and NE infusion

Pt.	Age and sex	Phase	Brach. B.P. (mm. Hg)	Digital B.P. (mm. Hg)	Eff. mean dig. B.P. (mm. Hg)	Dig. blood flow (cc./cpr.²skin/min.)	Radius equivalent (cm. × 10⁻²)	Work of vasoconstriction (10³ ergs)	Rate of NE infusion (10⁻²mg./min.)	Work/mg./min. (10³ ergs/mg./min.)	Per cent change
24	31F	1A	154/108	158/102	105	0.39	2.9				
		1B	170/120	162/113	128	0.04	2.2	6.3			
		1C	200/130	184/114	125	0.30	2.7	1.6	0.84	189	
		2A	105/80	110/88	83	0.28	2.8				
		2B	150/90	152/92	106	0.13	2.5	2.0			
		2C	150/110	162/106	117	0.20	2.6	1.3	0.69	157	−17
25	60M	1A	126/86	120/80	88	0.13	2.3				
		1B	180/112	170/110	127	0.08	2.1	1.6			
		1C	180/120	180/118	135	0.08	2.1	1.6	0.78	200	
		2A	118/82	116/74	81	0.16	2.4				
		2B	156/90	152/88	102	0.16	2.4	1.9			
		2C	198/112	192/116	137	0.10	2.1	1.9	0.90	214	+7
26	27F	1A	130/90	130/86	88	0.27	2.8				
		1B	180/120	160/120	132	0.02	1.7	7.6			
		1C	190/120	176/120	126	0.29	2.6	0.72	0.91	79	
		2A	98/60	100/76	68	0.24	2.8				
		2B	124/82	132/90	99	0.14	2.5	1.5			
		2C	160/100	160/92	104	0.25	2.7	0.50	1.1	48	−39
27	49F	1A	104/80	98/66	72	0.12	2.4				
		1B	180/100	174/86	112	0.08	2.1	1.5			
		1C	200/110	184/106	129	0.08	2.1	1.5	0.84	182	
		2A	80/50	60/42	45	0.08	2.4				
		2B	128/80	92/62	69	0.07	2.2	0.59			
		2C	138/90	100/76	82	0.06	2.1	1.00	1.6	62	−67

be visualized as an activator of the reaction; in high concentration the ion probably would be inhibitory by virtue of suppression of some other concomitant ionic activation, whereas in low concentrations there would be less activation of the enzymatic process.

The other actions of chlorothiazide and its congeners are inconsistent, and probably represent complex hemodynamic effects produced by such factors as decreased plasma volume and decreased cardiac output, together with compensatory or permissive neurogenic reactions to such events. It is of interest that in normotensive subjects the blood pressure remains constant by virtue of hemodynamic effects counterbalancing each other, rather than by failure of the drugs to influence the cardiovascular system.

TABLE 5

BEFORE (1) AND AFTER (2) 10 MG. OF BENZYDROFLUMETHIAZIDE DAILY FOR TWO WEEKS IN THREE NORMOTENSIVE SUBJECTS

A = after vasodilatation, B = before vasodilatation, C = after vasodilatation and NE infusion

Pt.	Age and sex	Phase	Brach. B.P. (mm. Hg)	Digital B.P. (mm. Hg)	Eff. mean dig. B.P. (mm. Hg)	Dig. blood flow (cc./cpr.^{2}skin/min.)	Radius equivalent (cm. $\times 10^{-2}$)	Work of vasoconstriction (10^3 ergs)	Rate of NE infusion (10^{-2}mg./min.)	Work/mg./min. (10^3 ergs/mg./min.)	Per cent change
28	31F	1A	92/60	90/60	63	0.17	2.6				
		1B	124/70	122/80	90	0.10	2.4	0.95			
		1C	140/80	140/86	97	0.17	2.5	0.46	1.0	46	
		2A	96/60	92/66	64	0.26	2.9				
		2B	114/70	110/66	74	0.17	2.7	1.1			
		2C	136/80	108/72	74	0.17	2.7	1.1	2.0	53	+15
29	17M	1A	90/60	84/58	56	0.24	3.0				
		1B	116/70	102/68	72	0.17	2.7	1.3			
		1C	130/86	138/80	85	0.29	2.9	0.37	0.8	41	
		2A	82/50	72/50	47	0.25	3.1				
		2B	110/64	98/60	64	0.20	2.9	0.84			
		2C	136/80	134/84	89	0.28	2.9	0.84	0.85	99	+141
30	17M	1A	110/70	106/64	67	0.27	2.9				
		1B	126/80	126/78	92	0.04	2.3	3.6			
		1C	134/80	130/76	84	0.24	2.8	0.52	1.4	37	
		2A	98/60	90/40	47	0.27	3.2				
		2B	124/70	104/48	57	0.25	3.1	0.38			
		2C	130/74	102/62	65	0.24	3.0	1.0	1.4	74	+100

It is also apparent, despite the small number of cases, that with equipotent dosage the effects of the congeners of chlorothiazide on the digital circulation are not significantly different from those of the parent drug.

Summary

(1) Chlorothiazide and its congeners were administered to normotensive subjects and patients with hypertension, and their effect observed by means of digital circulatory tests.

(2) In the hypertensive subjects the only consistent changes produced were a decrease in blood pressure and in digital vascular reactivity to *l*-norepinephrine (NE), whereas in the normotensive subjects there was no change in the blood pressure and usually an increase in NE reactivity.

(3) Complex hemodynamic changes differing from case to case accounted for the decrease or the absence of change in blood pressure in both groups.

(4) The relation between NE reactivity and the blood pressure in these groups after treatment with these sodium-depleting drugs may be explained by postulating an optimum concentration of the ion, below and above which smooth muscle contractility is stimulated or by considering sodium to be an ionic activator of an enzyme system.

TABLE 6

BEFORE (1) AND AFTER (2) 10 MG. OF BENZYDROFLUMETHIAZIDE DAILY FOR TWO WEEKS IN THREE HYPERTENSIVE SUBJECTS

A = after vasodilatation, B = before vasodilatation, C = after vasodilatation and NE infusion

Pt.	Age and sex	Phase	Brach. B.P. (mm. Hg)	Digital B.P. (mm. Hg)	Eff. mean dig. B.P. (mm. Hg)	Dig. blood flow (cc./cpr.^{2}skin/min.)	Radius equivalent (cm. $\times 10^{-2}$)	Work of vasoconstriction (10^3 ergs)	Rate of NE infusion (10^{-2} mg./min.)	Work/mg./min. (10^3 ergs/mg./min.)	Per cent change
31	57F	1A	154/94	156/90	109	0.07	1.8				
		1B	264/124	194/114	141	0	0	7.8			
		1C	250/136	212/126	153	0.05	1.7	3.4	0.48	710	
		2A	196/110	170/110	125	0.11	2.1				
		2B	220/122	188/120	141	0.04	1.7	2.1			
		2C	264/126	226/126	157	0.04	1.7	2.1	0.79	260	−63
32	41F	1A	140/90	138/88	93	0.28	2.7				
		1B	156/96	144/88	99	0.19	2.6	0.67			
		1C	190/108	174/100	120	0.18	2.5	0.50	0.82	183	
		2A	96/66	86/60	58	0.26	3.0				
		2B	120/70	110/70	76	0.16	2.8	0.95			
		2C	140/90	118/82	83	0.27	2.9	0.46	0.88	52	−72
33	25F	1A	110/74	96/70	68	0.27	2.9				
		1B	156/100	126/90	100	0.04	2.1	4.9			
		1C	150/100	148/96	107	0.15	2.5	2.3	1.3	180	
		2A	106/70	90/62	61	0.23	2.9				
		2B	120/80	108/70	81	0.05	2.3	3.0			
		2C	156/100	144/90	101	0.17	2.6	1.5	0.82	178	−1

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THE ROLE OF DIURETICS IN THE MANAGEMENT OF HYPERTENSION

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A number of diuretic agents such as the mercurials and benzothiadiazines have been shown to be useful in the clinical management of arterial hypertension, especially in combination with other drugs. The exact manner in which these agents lower blood pressure has not been clearly established. However, studies in our laboratory have indicated that the antihypertensive effect of these agents is not due solely to sodium depletion.[1-3] The metabolic studies that support such a conclusion are reviewed in the present report. In addition, the antihypertensive actions of a new group of diuretic compounds, the steroidal lactones, are described.[3-5]

Procedure and Results

The metabolic study shown in FIGURE 1 was undertaken in a subject with uncomplicated essential hypertension to determine whether sodium depletion was directly responsible for the antihypertensive action of chlorothiazide.[3]

During a moderately high sodium intake of 163 mEq./day, chlorothiazide produced an appreciable reduction in the blood pressure that was associated with a net sodium loss of 242 mEq. and a weight reduction of 1 kg. When fluorohydrocortisone, a mineralocorticoid, was added to the chlorothiazide regimen, it restored the sodium balance to control values but did not block the antihypertensive effect of the chlorothiazide. The retention of sodium caused by fluorohydrocortisone was accompanied by a further depression of serum potassium.

These and similar studies in other patients indicate that the hypotensive action of chlorothiazide is not solely or chiefly due to sodium depletion. However they do not exclude fluid volume changes as a cause of the antihypertensive action of chlorothiazide, especially since the weight reduction caused by chlorothiazide was not corrected by fluorohydrocortisone. In view of these findings and those of other workers,[6,7] suggesting that the antihypertensive effect of chlorothiazide might be due to a reduction in plasma volume, it was decided to study the effects of changes in plasma volume on the blood pressure responses to chlorothiazide. The results of one of these studies is shown in FIGURE 2. Shortly after the administration of chlorothiazide there was an appreciable reduction in blood pressure, which was associated with a significant decrease in plasma volume and weight. When plasma volume was then reexpanded to and above control values by infusing 500 cc. of plasma, the antihypertensive effect of chlorothiazide was maintained. The additional infusion of 1500 cc. of isotonic saline also had no striking effect on the blood pressure. The total sodium content of these parenterally administered fluids was 286 mEq., more than adequate to compensate for the net loss of sodium produced by chlorothiazide prior to their administration. These and similar observations in other patients indicate that neither a reduction of plasma value nor of body sodium is directly responsible for the early hypotensive action of chlorothiazide.

Measurements of body fluids and electrolytes before and after prolonged chlorothiazide treatment also have indicated that the late antihypertensive effect of chlorothiazide is not due solely to sodium or fluid volume depletion.[1, 2, 5] Similar observations have recently been reported by other workers.[8, 9]

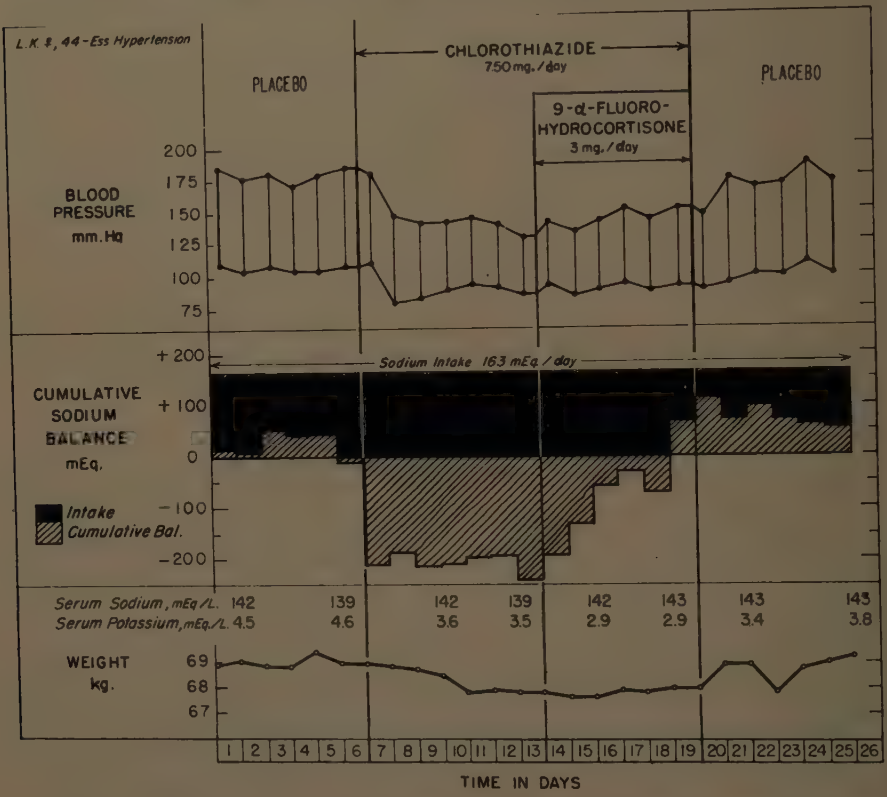

FIGURE 1. The effect of 9-α-fluorohydrocortisone on the diuretic and hypotensive actions of chlorothiazide in a subject with essential hypertension. In each balance figure, the blood pressure that is plotted daily is the average value of six or more determinations. The daily intake of sodium or potassium is represented by a solid area that is measured upward from the zero base line. The cumulative negative sodium or potassium balance is shown by a hatched or cross-hatched area below the zero base line. The cumulative positive sodium or potassium balance is plotted above the zero base line. Weight in kilograms is shown at the beginning of each day.

As shown in TABLE 1, chlorothiazide given continuously for four to eight weeks produced a significant reduction in blood pressure, but did not alter significantly the total exchangeable sodium (Na^{24} space) or the extracellular fluid volume ($S^{35}O_4$ space). However, the total exchangeable potassium (K^{42} space) was reduced during such therapy. These observations suggest that the initial losses of body sodium and fluids caused by chlorothiazide are slowly corrected during continued treatment with the drug. Some of the possible mechanisms that might operate to offset the early diuretic effects of chlorothiazide include a reduction in glomerular filtration rate and an increase in aldosterone activity.

Chlorothiazide and its derivatives appear to have a selective antihypertensive action in arterial hypertension even when body fluid and electrolyte composition are not altered significantly in this condition. TABLE 2 shows that serum osmolarity, extracellular fluid volume ($S^{35}O_4$ space), and total exchangeable

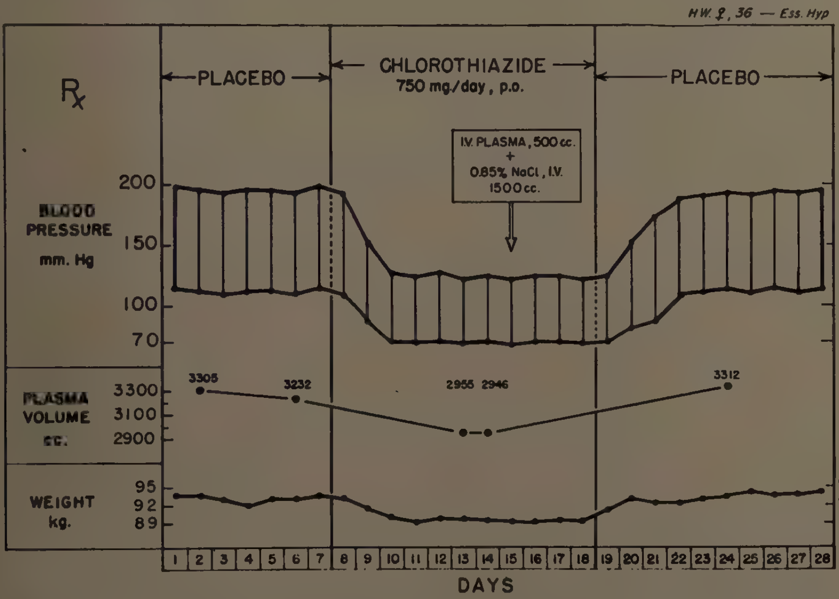

FIGURE 2. The effect of plasma volume on the antihypertensive action of chlorothiazide

TABLE 1

THE EFFECT OF CONTINUOUS CHLOROTHIAZIDE THERAPY ON BODY FLUID AND ELECTROLYTE COMPOSITION IN 12 SUBJECTS WITH ARTERIAL HYPERTENSION

Procedure	Weight (kg.)	Blood pressure (mm. Hg)	E.C.F. (% body wt.)	Exchangeable Na (mEq./kg. B.W.)	Exchangeable K (mEq./kg. B.W.)
Control	63.6	205/122 (±19) (±11)	13.9 (±1.2)	37.8 (±4.1)	32.8 (±5.4)
Chlorothiazide (375–750 mg./day for 4–8 weeks)	64.4	161/93 (±11) (±7)	13.5 (±1.4)	37.4 (±4.0)	29.9 (±4.8)
P value	0.3	<0.01	0.2	0.6	0.02

sodium (Na_e) and potassium (K_e) are not significantly different in subjects with uncomplicated essential hypertension as compared with control subjects. In view of the apparent selective action of chlorothiazide and mercurial diuretics in hypertensive subjects it has been postulated that diuretics might lower the blood pressure by interfering with some pressor mechanism, possibly arising in the kidney.[2,3] It is interesting that Judson and Helmer have reported recently that antihypertensive drug therapy is capable of reducing the vasoconstrictor activity in the renal vein blood of some hypertensive patients.[10]

The experiments shown in FIGURE 3 indicate that the hypotensive effect of chlorothiazide is not necessarily accompanied by an alteration in the reactivity of the blood pressure to norepinephrine. In FIGURE 3 the increases in blood pressure caused by continuously infused norepinephrine after one week of chlorothiazide treatment were considerably less than those caused by the same doses of norepinephrine during the control period. However after more prolonged chlorothiazide treatment (eight weeks) the blood pressure, although still reduced, again became as responsive to infused norepinephrine as it had been during the control period. The changes in reactivity of the blood pressure during chlorothiazide treatment in these and other experiments appear to parallel the changes of body sodium rather than those of any of the other electrolytes measured.

TABLE 2

BODY FLUID AND ELECTROLYTE COMPOSITION IN ESSENTIAL HYPERTENSION

Group	No. of cases	Age (yrs.)	Weight (kg.)	B.P. (mm. Hg)	E.C.F. ($S^{35}O_4$ space) (% body wt.)	Serum osmolarity (mOsm./l.)	Na_e per body wt. (mEq./kg.)	K_e per body wt. (mEq./kg.)
Controls	20	46 (±9)	75 (±14)	120/75 (±12/8)	14.7 (±1.5)	286 (±4.5)	36.2 (±4.1)	34.6 (±7.1)
Hypertensives	20	49 (±10)	75 (±12)	202/122 (±27/13)	14.1 (±1.1)	288 (±5.5)	37.1 (±5.0)	35.9 (±7.9)
P		0.3	>0.09	<0.01	0.2	0.1	0.5	0.5

A number of other sulfonamide diuretics have been studied in arterial hypertension. They include hydrochlorothiazide, hydrotrichlorothiazide, flumethiazide, hydroflumethiazide, benzydroflumethiazide, and chlorthalidone. The mode of action of these drugs on the blood pressure appears to be similar to that of chlorothiazide. Their long-term effect on the blood pressure and serum electrolytes also appears to be comparable to that of chlorothiazide.

The metabolic study shown in FIGURE 4 in a subject with uncomplicated essential hypertension was undertaken with SC 8109, an aldosterone antagonist, because of the possibility that an increased excretion of aldosterone might account for the absence of sodium depletion during continued chlorothiazide treatment.[3]

When oral chlorothiazide was given alone, it produced a moderate reduction in blood pressure that was associated with a net sodium loss of 150 mEq. After a further continuation of chlorothiazide administration failed to produce any further decrease in the blood pressure and sodium balance, SC 8109 was added to the treatment. It was given for four days in combination with chlorothiazide, and caused further reductions of blood pressure and body sodium; the net loss of sodium increased to 300 mEq. On withdrawing SC 8109 while continuing chlorothiazide, the blood pressure and sodium balance returned to pre-SC 8109 levels. The latter part of the experiment with fluorohydrocortisone is similar to that described in FIGURE 1. When fluorohydrocortisone was added to chlorothiazide it corrected the negative sodium balance previously caused by chlorothiazide to a positive balance, but did not abolish the antihypertensive effects of chlorothiazide. It is noteworthy that in this experiment as in the previous one (FIGURE 1) fluorohydrocortisone augmented the hypopotassemic effect of chlorothiazide.

H.W.♀,34

	Duration	B.P.	Wgt.(kg.)	Body Na /kg. wgt.	Serum (mEq./l.)			
					K	Na	CO_2	Cl
Control	4 Wks.	180/95	89.8	32.5	4.9	147	26	105
Early ℞	1 Week	145/95	88.0	30.2	3.5	147	26	105
Late ℞	8 Wks.	150/90	89.3	32.7	3.6	145	28	102

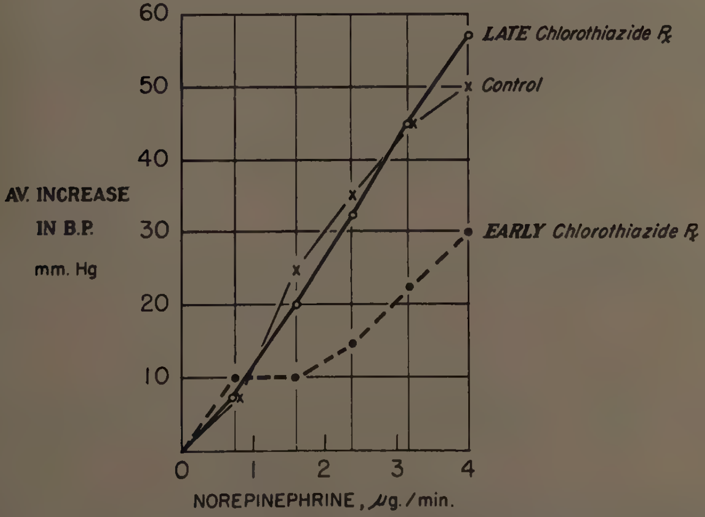

FIGURE 3. The effect of early and late chlorothiazide treatment on the reactivity of the blood pressure to increasing doses of infused norepinephrine in a subject with essential hypertension.

These as well as other metabolic studies indicate that the steroidal lactones and aldosterone antagonists are capable of exerting an antihypertensive as well as a diuretic action. They also support the hypothesis that the diuretic effects of chlorothiazide tend to be counteracted by an increase in aldosterone activity, whereas the hypokalemic effects of chlorothiazide tend to be augmented by an increase in aldosterone activity.

The metabolic effects of a more potent steroidal antagonist, SC 9420 or spironolactone, are shown in a subject with uncomplicated hypertension in

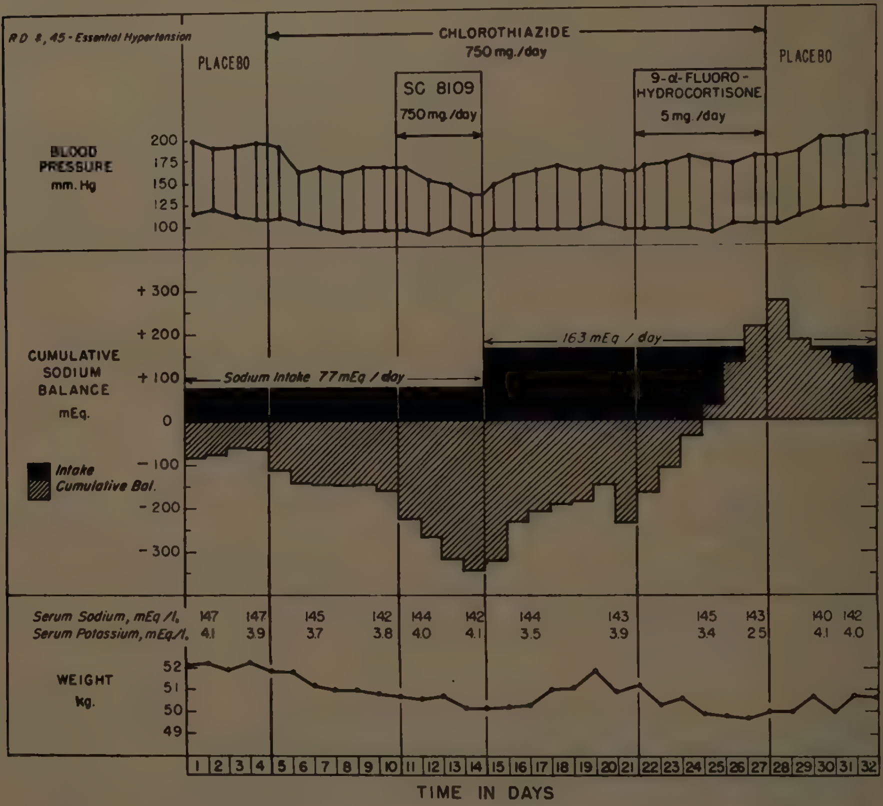

FIGURE 4. The effect of a steroidal lactone and antagonist (SC 8109) and 9-α-fluorohydrocortisone on the diuretic and hypotensive actions of chlorothiazide in a subject with essential hypertension.

FIGURE 5.[5] During a moderately high sodium intake of 145 mEq./day, SC 9420, alone, in a daily oral dosage of 300 mg., effectively reduced the blood pressure. The fall in blood pressure was gradual and appeared to parallel the loss of body sodium, which totaled 228 mEq. Accompanying the sodium diuresis there was a slight retention of potassium. Weight reduction also occurred during SC 9420 administration, but serum sodium and potassium, plasma volume, and creatinine clearance did not change. The infusion of 1000 cc. of isotonic saline on the 14th and again on the 15th metabolic days reduced the negative sodium balance, but did not increase the blood pressure. The blood pressure also was not increased *during* a second saline infusion, when the sodium balance was estimated to be close to zero. In FIGURE 6 the hypotensive effect of spironolactone (SC 9420) is shown to be associated not only with a negative sodium balance, but also with a reduction in plasma volume and creatinine clearance.[4,5] It is noteworthy that spironolactone continued to exert an antihypertensive effect even when the plasma volume was re-expanded to and above the control values on the 15th metabolic day by the infusion of 500 cc. of plasma. These and similar observations in other subjects suggest that the hypotensive action of spironolactone, similar to that of chlorothiazide, is not due solely to a reduction in body sodium or in plasma volume.

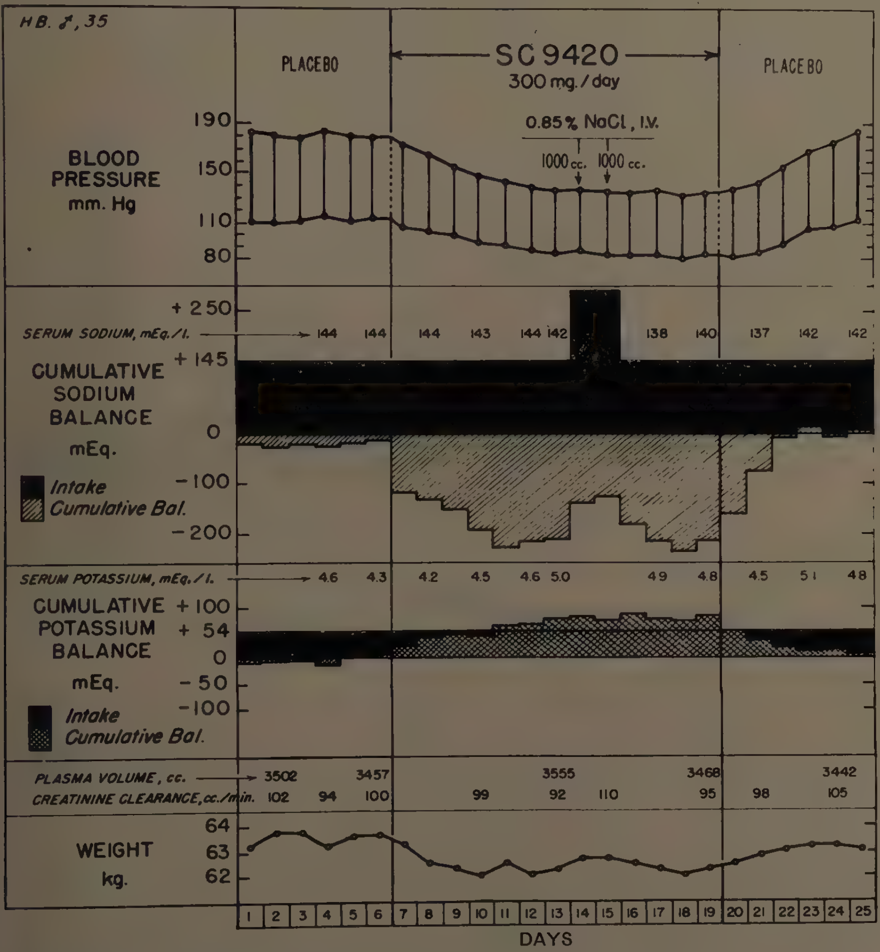

FIGURE 5. The effects of spironolactone (SC 9420) before and after infusions of saline in a subject with uncomplicated essential hypertension.

As shown in FIGURE 7, the effects of spironolactone on the sodium and potassium balances in a normal subject receiving a moderately high intake of sodium were comparable to those observed in hypertensive subjects. However, SC 9420 had no effect on the blood pressure. The latter part of the experiment in FIGURE 7 shows that when parenteral DOCA (desoxycorticosterone) was added to the regimen of SC 9420, it had no effect on the sodium and potassium balances although, when given alone, it caused retention of sodium and increased excretion of potassium. These and other similar findings indicate that the steroidal lactones are steroidal antagonists that cause a sodium diuresis even during a moderately high sodium intake, in normal as well as in hypertensive subjects. Although these observations might suggest a nonspecific diuretic action of the drug, they are consistent with the hypothesis that the steroidal lactones antagonize normal as well as increased amounts of aldosterone and mineralocorticoids.

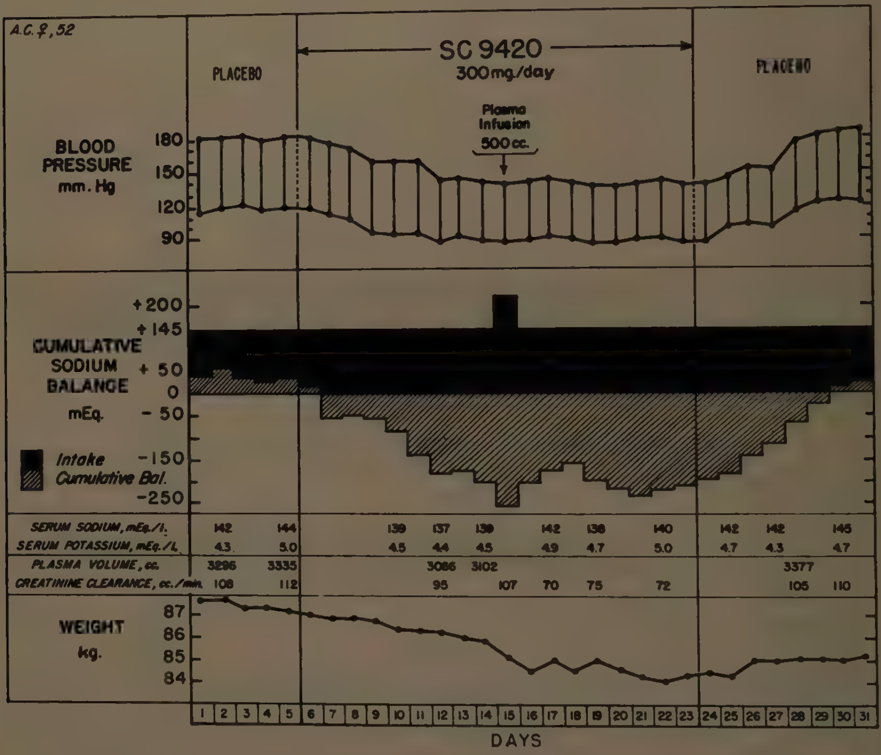

FIGURE 6. The effects of spironolactone (SC 9420) before and after the infusion of plasma in a hypertensive subject.

The clinical effects of spironolactone in a subject with uncomplicated essential hypertension are shown in FIGURE 8. A combination of reserpine, hydralazine, and hydrochlorothiazide had produced a moderate reduction in blood pressure.

However the patient experienced extreme weakness, which was associated with a marked depression of serum potassium to 2.2 mEq./l. Following the addition of spironolactone there was a further reduction in blood pressure, an increase in serum potassium to normal, and a complete disappearance of all symptoms. In the last part of the study satisfactory control of the blood pressure and serum electrolytes was achieved with spironolactone alone, as well as in combination with hydrochlorothiazide.

The clinical effects of spironolactone on the blood pressure of 37 hypertensive subjects, who received the compound continuously for 1 to 10 months during an unrestricted salt intake, are summarized in TABLE 3. When spironolactone was given alone it produced an appreciable reduction of blood pressure in about one half the subjects who also had previously responded to chlorothiazide. In combination with other antihypertensive drugs, including chlorothiazide, spironolactone caused a further reduction of blood pressure in three quarters of the subjects. The hypotensive action of spironolactone, unlike that of chlorothiazide, was gradual in onset. It usually occurred in one to two weeks, and was maximal in two to three weeks after the administration of the drug.

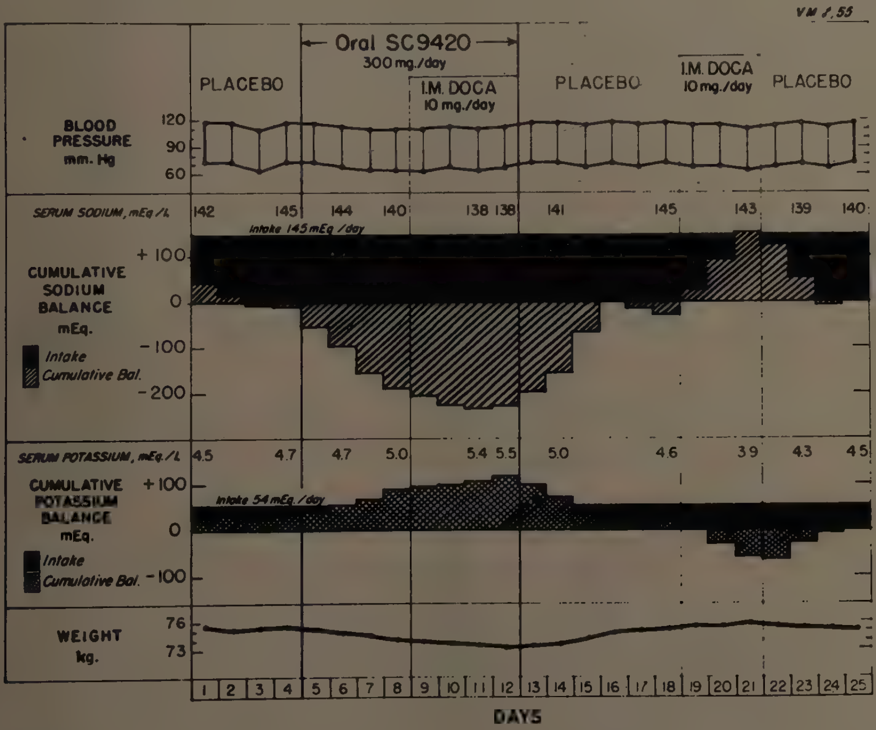

FIGURE 7. The effects of spironolactone and desoxycorticosterone (DOCA) in a normal subject.

The effect of spironolactone on serum sodium and potassium in 30 of the

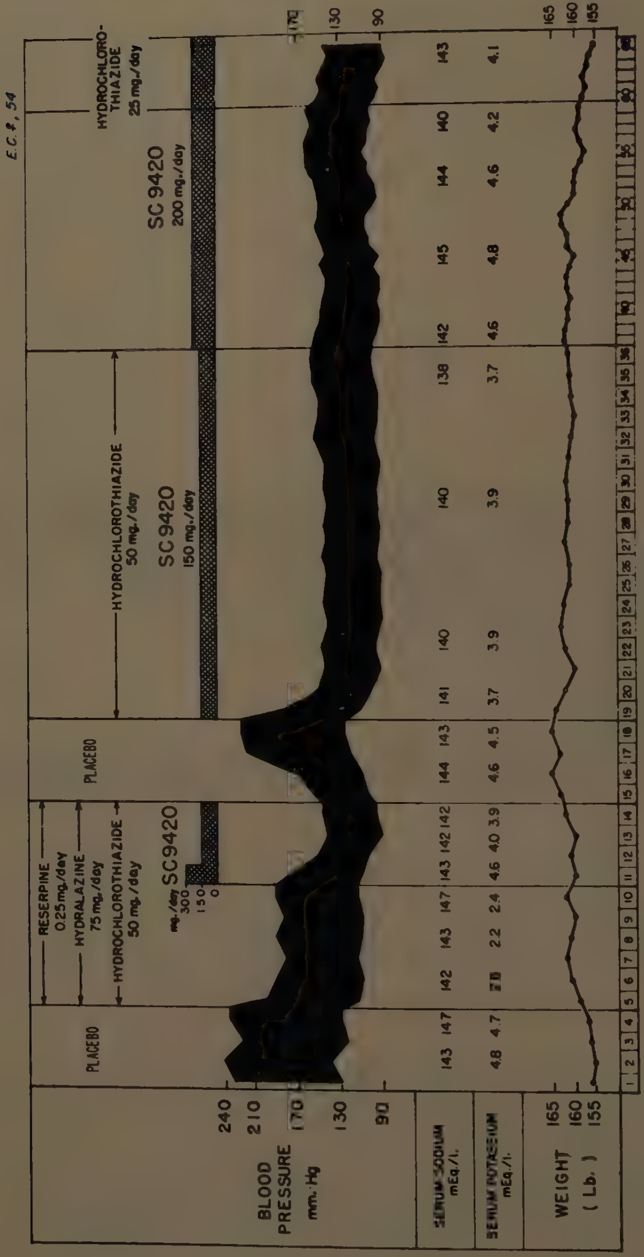

FIGURE 8. The clinical effects of spironolactone (SC 9420) in a hypertensive subject.

hypertensive subjects is summarized in TABLE 4. Spironolactone alone, in a usual dose of 300 mg./day, had no appreciable effect on serum sodium but did produce a slight rise in serum potassium that later decreased toward control levels during more prolonged administration of the drug. Before the addition of spironolactone, the chlorothiazides produced a depression of serum potassium by more than 0.4 mEq./l. in 60 per cent of the subjects, and to below 3.5 mEq./l., the lower range of normal, in 35 per cent of the cases. When spironolactone was then added to chlorothiazide, it increased and restored serum potassium to normal in almost every case. The effects of spironolactone given in combination with chlorothiazide on serum sodium were not striking except in one patient who developed hyponatremia.

TABLE 3

SPIRONOLACTONE (SC 9420) IN 37 HYPERTENSIVE SUBJECTS

Drugs	No. of cases	No. of responders	Average B.P. reduction (mm. Hg)	Range of B.P. reduction (mm. Hg)	Usual dosage (mg./day)	Dose range (mg./day)
Spironolactone	12	6	21/11	15–65/10–35	300	200–400
Other drugs + spironolactone	25	18	31/16	15–55/10–30	200	150–300

TABLE 4

THE EFFECT OF SPIRONOLACTONE (SC 9420) ON SERUM SODIUM AND POTASSIUM

	10 Cases		20 Cases		
	Control	Spironolactone	Control	Thiazide	Thiazide + spironolactone
Serum sodium mEq./l.	142 (139–145)	141 (136–144)	142 (138–147)	141 (137–145)	140 (134–142)
Serum potassium mEq./l.	4.5 (3.8–5.0)	4.8 (4.0–5.5)	4.4 (3.7–5.0)	3.6 (2.4–4.5)	4.4 (3.5–5.0)

Summary

The initial antihypertensive effect of the chlorothiazides and steroidal lactones is associated with a loss of body sodium and a contraction of plasma volume. However a simple reduction in body sodium or in plasma volume does not appear to be directly responsible for the hypotensive action of these agents, since acute experimental correction of these fluid and electrolyte deficits is not followed by a return of the blood pressure to anywhere near control levels. The late hypotensive effect of these agents likewise may occur without measurable decreases in total body fluids or electrolytes, or a reduced reactivity of the blood pressure to infused norepinephrine. The possibility that diuretics may lower the blood pressure by interfering with some arterial pressor mechanism has been suggested, although not proved.

While the mode of action of spironolactone on the blood pressure appears to be similar to that of chlorothiazide, it may be related to antisteroidal effects. The latter mode of action is consistent with the increased aldosterone excretion reported by Genest and others to occur in uncomplicated essential hypertension.[11,12]

The sulfonamide diuretics given in comparable diuretic doses over a prolonged period appear in general to be equally effective in reducing the blood pressure and to have comparable effects on the serum electrolytes. Spironolactone also is an effective antihypertensive agent, especially when given in combination with other antihypertensive drugs. It does not depress serum potassium but, on the contrary, corrects the hypokalemia produced by the usual diuretics.

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Discussion of the Paper

LEO SCHAMROTH (*Mercy Hospital, Baltimore, Md.**): The paper by Hollander is most interesting and stimulating. One of the most significant points it introduces is the hypothesis that the thiazide derivatives have a specific antihypertensive action, an action quite divorced from their diuretic effect and as yet unexplained. During the past year my associates and I have been evaluating the effect of one of these thiazide derivatives, benzydroflumethiazide (Naturetin), in the treatment of essential hypertension. Our results thus far have supported very strongly the correctness of the hypothesis presented by Hollander, namely, that the thiazide derivatives have a specific antihypertensive action.

Our investigation was conducted with 30 patients with essential hypertension who were being treated as outpatients. These patients were carefully screened to exclude renal disease, were not edematous, and were given no other medication during the trail. Furthermore, the study was designed to eliminate in so far as possible the influence of all extraneous factors that could be controlled and therefore to ensure that the effects seen were due exclusively to the administered medication. The details of procedure regarding the drug administration and the handling of patients were so planned that subjectivity on the part of the investigator was minimized. Placebos were administered for a few weeks until a natural and stable base line was obtained. A period of several months followed during which the active drug was substituted for the placebo. Finally, there was a period of return to placebo, this phase being regarded as an important part of the trial and essential to a proper evaluation of the results.

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Our results indicated that benzydroflumethiazide had a satisfactory antihypertensive action in 70 to 80 per cent of our cases (TABLE 1). At least 40 per cent of the patients manifested a fall of 20 mm. Hg or more in diastolic pressure. The greatest falls in pressure occurred in those patients with the highest initial levels. The antihypertensive effect was obtained with dosages varying from 10 to 40 mg. benzydroflumethiazide daily, taken in 2 divided doses. It was thought, however, that for the antihypertensive effect of this drug to be demonstrated with any degree of confidence a return to pretreatment levels should occur with the substitution of the second placebo regimen. This return was manifested in all cases in which the drug was effective in producing a fall in blood pressure.

TABLE 1
EFFECT OF NATURETIN IN A SERIES OF 23 HYPERTENSIVE PATIENTS

Response	Fall in diastolic B. P. (mm. Hg)	No. of patients
Excellent	>20	10 (43.5%)
Good	10 to 20	9 (39.1%)
Little or none	<10	4 (17.4%)

In Dallas, Texas (November 1959), where I presented an interim report on our work, some surprise was expressed at the high levels of our dosage. It was intimated that the same effects, if any, would have been elicited by 10 mg./day and that, if the effect were not obtained with 10 mg., any further increases in dosage would be futile. We have since paid particular attention to this aspect of the problem and must repeat our previous observation, namely, that in some cases it is necessary to go as high as 40 mg./day before the desired effect is obtained. This confirms the old adage that the optimal dose of a drug is the dose that produces the desired effect with a minimum of side reaction. It was noted, too, that maximal reductions in blood pressure usually took from two to three weeks to develop. In some cases, however, there was an initial sharp drop in blood pressure within the first week. It is significant that these cases usually had a noticeable drop in weight.

Most patients manifested some degree of weight loss, this loss averaging about 5 lb. It should be emphasized, however, that in the majority of cases there was no correlation whatsoever between weight loss and blood pressure fluctuations either during the administration of the drug or when the placebo was substituted.

It appears from these observations that the action of this drug is twofold: an initial drop in pressure may occur which is due in all probability to the diuretic effect, and a later fall may be seen, which is most probably due to a specific antihypertensive action.

There was no significant electrolyte disturbance (TABLE 2). Such variations as were noted in potassium blood levels were well within the standard error of laboratory technique. Many of our patients showed significant increases in blood uric acid levels while on the drug, but none of them exhibited any of the clinical manifestations of gout.

TABLE 2

CHANGES IN SERUM ELECTROLYTES AFTER 4 TO 8 WEEKS OF TREATMENT WITH NATURETIN

	Potassium (mEq./l.)		Sodium (mEq./l.)		Chloride (mEq./l.)	
	Increase	**Decrease**	**Increase**	**Decrease**	**Increase**	**Decrease**
	0.22	0.75	11.3	1.2	5.1	1.1
	0.40	0.18	19.3			5.4
	0.05	0.49	6.6			6.6
	0.06		4.3			12.5
	0.36		2.5			4.5
	1.36		13.2			1.4
	0.40		9.8			7.6
	0.43		9.5			7.7
			4.0			12.0
			13.0			0.5
Mean	0.41	0.47	9.35	1.2	5.1	5.93
No. of cases	8	3	10	1	1	10
Standard error	±0.3	±0.3	±0.25	±0.25	±0.25	±0.25

Perhaps most noteworthy of all was the complete absence of any side effects. These were neither volunteered by the patient nor elicited by close questioning. There were no skin reactions, gastrointestinal or genitourinary manifestations; nor was there joint involvement, even with dosage as high as 40 mg./day. Indeed, most or nearly all of the patients reported a feeling of well-being associated with the alleviation of symptoms due to the hypertension.

The feeling of well-being is very apparent when contrasted with the status of those patients who receive ganglion-blocking agents. All of us who have had experience with the ganglion-blockers will have noted that patients usually feel "under the weather" while on this form of therapy. This may be due to the difficulty of gauging correct dosage. In any event, it has been facetiously said that these drugs make one as weak as a kitten, as constipated as an owl, as blind as a bat, and as impotent as a capon. I do not for one moment suggest that the thiazide derivatives are a substitute for the ganglion-blocking agents; it should be stressed, however, that agents of this nature, such as benzydroflumethiazide, with an absence of any significant side reaction, provide a very useful addition to the antihypertensive armamentarium. These agents represent a significant advance in antihypertensive therapy, and it appears that they are indicated in all grades of essential hypertension. They are also useful as adjuvant therapy in cases requiring ganglionic-blocking agents and in which ganglion-blockers are contraindicated, as in severe myocardial and cerebral arterial disease. When used with the blocking agents, the diuretic effect of the thiazides is additive and usually beneficial.

The interest in the thiazide drugs stems from their effectiveness and minimal side reactions and, as Hollander suggests, their specificity of action in hypertension. I believe that we may look forward to the day when, by juggling the basic structure of the thiazide radical, an analogue will be compounded that will have only hypertensive action and no diuretic action whatsoever.

CLINICAL EVALUATION OF GUANETHIDINE IN HYPERTENSION

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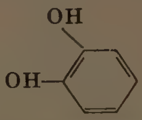
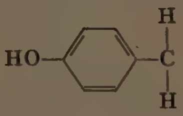
The amidoxime, (2-[octohydro-1-azocinyl]-ethyl)-guanidine sulfate, was developed as an antihypertensive agent and given the generic name guanethidine.[1,2] This followed the preliminary work with other amidoximes by Mull and his associates.[3] The main chemotherapeutic action of these substances is due to the blockade of the sympathetic nervous system, apparently at the site of their peripheral terminals.[2] It should be noted that they enhance the pressor response of the pyrocatechol derivates, which contain the structure



and block the pressor effect of the neurosympathomimetics containing the structure



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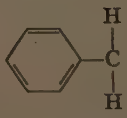

Norepinephrine, epinephrine, synephrine, and neosynephrine are among those amines whose pressor action is augmented. Amphetamine, phenylethylamine, methamphetamine, tyramine, and paredrine are among those whose pressor action is blocked.[4]

Clinical evaluation of guanethidine has demonstrated that it lowers the blood pressures of hypertensive individuals.[5-8] The purpose of the present study is to evaluate guanethidine as an antihypertensive agent by using the double-blind technique.

Method

Selection of patients. Outpatients attending the hypertension clinic at the Los Angeles County General Hospital for a period of not less than six months were selected for this study. Those eliminated from this group were persons who previously had been diagnosed as having "malignant" or accelerated hypertension, those with a serum urea nitrogen above 30 mg. per cent, or those who had been in serious cardiac decompensation as the result of hypertensive heart disease and whose blood pressures were now controlled by therapy. Forty-one patients started on the double-blind evaluation.

Clinic procedures and double-blind technique. All medications were stopped for at least a consecutive 4-week period. During this interval every patient had a chest X ray, electrocardiogram, hemoglobin, white blood count, urinalysis, serum urea nitrogen, and serum glutamic-oxaloacetic transaminase (SGOT) determination. These laboratory procedures, except for the electrocardiogram and chest X ray, were repeated at the minimum of every 4 weeks throughout the study. The supine or standing diastolic pressure was required to be 110 mm. Hg or more before a patient was included in the double-blind evaluation. All patients were seen at 2-week intervals.

One 25 mg. tablet of guanethidine and an identical placebo tablet were used. A single daily dose with breakfast was given. Each patient was started on one-half tablet per day, and this was increased at the rate of one-half tablet per week until one or more of the following events took place: (1) the systolic pressure reached 150 mm. Hg; (2) the diastolic pressure reached 90 mm. Hg; or (3) side effects necessitated a reduction or stabilization of dosage.

The physician who dispensed the medications did so in a room that was separate from the clinic. He was not in contact with the other personnel during the time the clinic was in progress. His records were kept confidential until the study was terminated. He did not participate in the evaluation of the patients. Conversely, those involved in evaluating the patients did not know which form of therapy was being given. The dosage of medication and written instructions were given to the patients by the physicians doing the evaluation. The double-blind evaluation was carried out for a 12-week period.

The method of measuring the blood pressure was as follows. Six curtained booths, which contained examining tables, were used. The patients were taken in the order in which they registered. After being recumbent for at least 10 min., the blood pressure was measured in the left arm with an aneroid sphygmomanometer. This was repeated with the patient in the sitting and then the standing positions. The same sphygmomanometer was used throughout, and it was calibrated with a mercury manometer. Three medical residents took the blood pressures in rotation, each taking an entire clinic visit. The previous readings were not available to them at this time. The patients were questioned for side effects only in general terms.

Statistical methods. The physician who dispensed the medications made a random list of all patients in the study and selected alternate patients to whom guanethidine was given. An identical placebo tablet was given to the remaining patients.

The standard error of the difference between two means, using t values with appropriate degrees of freedom, was used to ascertain the probability of whether any changes in the arithmetical means, designated as $\bar{x}$, of the systolic and diastolic pressures were due to random fluctuations of the sample. The probability (P) of 0.05 or less was considered significant. The formula $s_D = s'\sqrt{(N_1 + N_2)/N_1N_2}$ was utilized to determine the standard error (s_D) of the difference, where s' designates the estimated standard deviation of the population and N_1 and N_2 represent the number of observations within each sample. The formula used to find s' was

$$s' = \sqrt{\frac{\left[\Sigma x_1^2 - \frac{(\Sigma x_1)^2}{N_1}\right] + \left[\Sigma x_2^2 - \frac{(\Sigma x_2)^2}{N_2}\right]}{N_1 + N_2 - 2}}$$

where x_1 and x_2 represent an observation (blood pressure) within a sample. The t values were found by using the formula $t = (\bar{x}_1 - \bar{x}_2)/s_D$ where $\bar{x}_1$ and $\bar{x}_2$ represent the arithmetical means of the groups that were compared.

All supine and standing systolic and diastolic blood pressure measurements for the initial 6-week and for the entire 12-week period were utilized for the statistical analysis (APPENDIX, TABLES 1A to 8A). The mean pressures of the placebo- and guanethidine-treated groups were compared with one another, and the mean pressures of the placebo- and of the guanethidine-treated groups were, in turn, compared with the corresponding blood pressures of the entire group of 41 patients at the onset of the study.

Results

Forty-one patients were selected for the double-blind evaluation. Twenty were given guanethidine, while 21 were in the placebo group. There were 28 females and, of the total of 41, 31 were Negroes. The age ranged from 30 to 72 years, with a mean of 52.

One individual was dropped from the guanethidine-treated group after 2 weeks of therapy because of severe angina. No other patients in this group were lost from the study during the 12-week interval that comprised the double-blind evaluation.

One patient was lost from the placebo group 6 weeks after the double-blind procedure had been initiated and he could not be traced. His mean standing diastolic pressure to this point was 105 mm. Hg. Three others from the placebo group were dropped from the series after 8 weeks of the double-blind evaluation, one because of intractable nausea, the other two because of severe headaches. These latter 3 patients attributed their symptoms to the therapy and they refused to continue the placebo medication. Their mean standing diastolic pressures to this point were 127, 113, and 119 mm. Hg respectively. A fifth patient was dropped after 10 weeks of placebo treatment because of a mean standing diastolic pressure of 156 mm. Hg and the appearance of retinal hemorrhages. These 5 patients, who were lost from the placebo group, had a mean standing diastolic pressure of 126 mm. Hg, well above the mean for the placebo group as a whole. Therefore their elimination from the latter part of the study should not bias the results in favor of guanethidine as an antihypertensive agent.

Diastolic Pressures Responses

At the onset of the study, the diastolic arithmetical means of the combined group, consisting of 41 patients, were 116 mm. Hg for both the supine and standing pressures, with a standard deviation of 25 for the supine pressure and 22 for the standing pressures. The respective standard errors were 4.0 and 3.5. The mean pressures for the 20 patients who subsequently were to comprise the guanethidine-treated group were 117 mm. Hg supine and 119 mm. Hg standing. The mean pressures for the 21 patients who were to make up the placebo group were 116 mm. Hg supine and 113 mm. Hg standing.

During the first 6 weeks of the double-blind study, the diastolic mean pressures for the guanethidine-treated group were 111 mm. Hg supine and 101 mm. Hg standing, while the corresponding means for the placebo group were 118 mm. Hg supine and 117 mm. Hg standing. For the entire 12 weeks of the double-blind evaluation, the means for the actively treated group were 108 mm. Hg supine and 96 mm. Hg standing, and the comparable means for the placebo group were 116 mm. Hg supine and 115 mm. Hg standing. During the last 6 weeks of the study, the means for the guanethidine-treated group were 105 mm. Hg supine and 92 mm. Hg standing, while those for the placebo group were 113 mm. Hg supine and 112 mm. Hg standing (FIGURE 1).

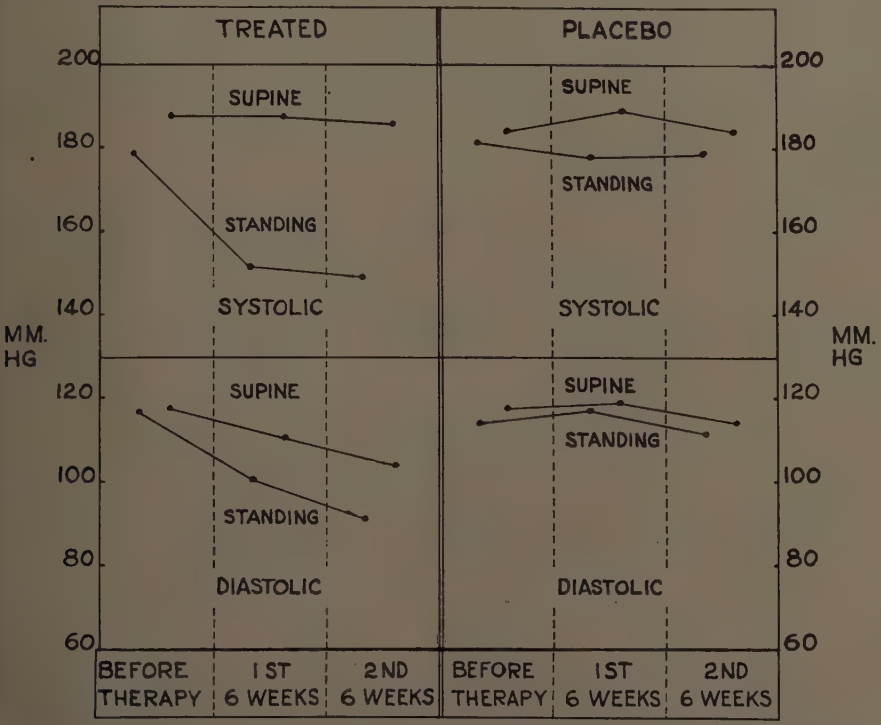

FIGURE 1. The mean supine and standing systolic and diastolic blood pressures of the guanethidine-treated and placebo groups.

The mean standing diastolic pressures of the guanethidine-treated group were significantly reduced during the first 6- and the entire 12-week period of treatment, when compared with the standing mean diastolic pressures of the placebo group for comparable intervals, and when compared with the standing diastolic mean of the entire group at the onset of the study ($P < 0.01$).

When the mean supine diastolic pressure of the guanethidine-treated group was compared statistically with the corresponding pressure of the placebo group, a significant drop was found in the guanethidine-treated group for the initial 6 weeks ($P < 0.05$) and for the entire 12-week period ($P < 0.01$). This is summarized in TABLE 1. Comparison of the supine diastolic pressures of the guanethidine-treated patients with the corresponding pressures at the onset of the study for the entire 41 patients, however, failed to reveal that this drop was significant during the first 6-week period of the evaluation. A significant drop ($P < 0.05$) was found when the data for the entire 12-week period were utilized (TABLE 2). The reasons for these conflicting results during the first 6 weeks of the double-blind study will be subsequently discussed.

Table 1

Standard Error of the Difference between the Means, Supine and Standing Diastolic Pressures (mm. Hg)*

Comparison of the Placebo with the Guanethidine-Treated Group

	Before therapy		6 Weeks		12 Weeks		
	Supine	Standing	Supine	Standing	Supine	Standing	
P	>0.5	0.1 to 0.5	0.05 to 0.01	<0.01	<0.01	<0.01	
t_e	0.13	0.84	2.11	5.3	3.2	6.5	
s_D	7.7	7.2	3.3	3.0	2.5	2.9	
s'	24.7	23	18.3	16.8	19.2	21.9	
$\bar{x}$	117	119	111	101	108	96	Treated
	116	113	118	117	116	115	Placebo

* $\bar{x}$ = mean; s' = estimated standard deviation of the population; s_D = standard error of the difference; t_e = tabular value of t; P = probability that the differences were random fluctuations of the sample, with 1 = 100 per cent. P of 0.05 or less was considered significant.

Table 2

Standard Error of the Difference between the Means, Supine and Standing Diastolic Pressures (mm. Hg)*

Comparison of the Diastolic Means of the Placebo and the Guanethidine-Treated Group with the Diastolic Means of the Entire Group at the Onset of the Study†

	6 Weeks		12 Weeks		6 Weeks		12 Weeks		
	Placebo				Treated				
	Supine	Standing	Supine	Standing	Supine	Standing	Supine	Standing	
P	>0.5	>0.5	>0.5	>0.5	0.5 to 0.1	<0.01	<0.05	<0.01	
t_e	0.49	0.25	0	0.29	1.09	3.84	2.0	4.4	
s_D	4.1	3.9	3.6	3.4	4.6	3.9	4.1	4.5	
s'	20.6	19.7	19.7	18.6	22.5	19.3	22.5	25.1	
$\bar{x}$	118	117	116	115	111	101	108	96	After ℞
	116	116	116	116	116	116	116	116	Before ℞

* Key to symbols as in TABLE 1.

† The means for the entire group prior to the study were 116 mm. Hg for both supine and standing diastolic pressures.

The supine and standing diastolic means of the placebo group showed no significant change during the initial six and the entire 12 weeks of the double-blind procedure, when they were compared with the means of the combined group at the onset of the study. These results are summarized in TABLE 2.

Systolic Pressures Responses

The arithmetical means of the systolic pressures of the combined group of 41 patients at the onset of the double-blind evaluation were 186 mm. Hg supine and 181 mm. Hg standing. The standard deviations were 25 and 22 respectively, with standard errors of 4.0 and 3.5. The means for the 20 patients who subsequently were to comprise the guanethidine-treated group were 187 mm. Hg supine and 179 mm. Hg standing, while the means of the 21 patients who were to comprise the placebo group were 185 mm. Hg supine and 183 mm. Hg standing.

TABLE 3

STANDARD ERROR OF THE DIFFERENCE BETWEEN THE MEANS, SUPINE AND STANDING SYSTOLIC PRESSURES (MM. HG)*

Comparison of the Placebo with the Guanethidine-Treated Group

	Before therapy		6 Weeks		12 Weeks		
	Supine	Standing	Supine	Standing	Supine	Standing	
P	>0.5	>0.5	>0.5	<0.01	>0.5	<0.01	
t_e	0.25	0.56	0.38	4.3	0	6.5	
s_D	8.1	7.2	5.3	4.7	4.4	3.4	
s'	26	23	29.3	26	33.2	25.7	
$\bar{x}$	187 185	179 183	187 189	157 177	187 187	155 177	Treated Placebo

* Key to symbols as in TABLE 1.

During the first 6 weeks of the double-blind study, the systolic mean pressures for the guanethidine-treated group were 187 mm. Hg supine and 157 mm. Hg standing. The corresponding means for the placebo group were 189 mm. Hg supine and 177 mm. Hg standing.

After 12 weeks, the means for this entire interval of those patients treated with guanethidine were 187 mm. Hg supine and 155 mm. Hg standing. For the placebo group, these means were 189 mm. Hg supine and 177 mm. Hg standing. The systolic means for the last 6-week period of the double-blind study were 186 mm. Hg supine and 154 mm. Hg standing for the guanethidine-treated patients and 184 mm. Hg supine and 178 mm. Hg standing for the placebo group (FIGURE 1).

Using the standard error of the difference and the probabilities derived therefrom, the mean standing systolic pressure in the guanethidine-treated group showed a significant drop during the first 6- and the entire 12-week period of the double-blind evaluation ($P < 0.01$) when compared with the placebo group for similar time intervals (TABLE 3), and to the means of the entire group at the onset of the study (TABLE 4). No significant change was found in the supine mean systolic pressures of the guanethidine-treated group during this 12-week period by either comparison. Comparison of the blood pressures of the placebo group for the 12-week period of the evaluation, with the mean supine and standing systolic pressures at the onset of the study for the entire group of 41 patients revealed no significant difference (TABLE 4).

Dosage and Side Effects

The mean dosage of guanethidine after 6 weeks was 55 mg., with a range of 25 to 100 mg. After 12 weeks, the mean dosage was 56 mg., with a range of 25 to 100 mg.

While taking guanethidine, nausea occurred in two patients with associated diarrhea in one. These symptoms responded to anticholinergic drugs in one individual. However, in the other patient further increase in dosage was limited because of nausea. Fainting, presumably on the basis of postural hypotension, occurred a total of three times in two patients in the actively treated group. The frequency of disabling side effects appeared to be much less than with ganglionic blocking agents.

TABLE 4

STANDARD ERROR OF THE DIFFERENCE BETWEEN THE MEANS, SUPINE AND STANDING SYSTOLIC PRESSURES (MM. HG)*

Comparison of the Placebo and Guanethidine-Treated Groups with the Systolic Means of the Entire Group at the Onset of the Study

	6 Weeks		12 Weeks		6 Weeks		12 Weeks		
	Placebo				Treated				
	Supine	Standing	Supine	Standing	Supine	Standing	Supine	Standing	
P	>0.5	>0.5	>0.5	0.5 to 0.1	>0.5	<0.01	>0.5	<0.01	
t_ϵ	0.5	0.67	0.16	0.9	0.2	5.6	0.2	5.7	
s_D	6.0	6.0	6.3	4.4	5.2	4.3	4.9	4.6	
s'	29.7	29.9	34.8	24.2	25.7	21.2	27.3	25.5	
$\bar{x}$	189	177	187	177	187	157	187	155	After ℞
	186	181	186	181	186	181	186	181	Before ℞

* Key to symbols as in TABLE 1.

The hemoglobins, white blood counts, urinalyses, serum urea nitrogens, and SGOT levels did not change significantly. Ten patients were observed for as long as 18 weeks while they received guanethidine, and no abnormal alterations took place in any of the preceeding laboratory procedures.

Discussion

Comparison of the placebo group with the patients who received guanethidine was a more powerful test of significance, because of the greater number of observations available than for comparison of these groups individually with the mean blood pressures at the onset of the study of the entire group of 41 patients. Therefore a significant drop in the mean supine diastolic pressure for those patients who had taken guanethidine was revealed by one method but not by the other. It should be noted that both methods showed that this drop in the supine diastolic pressure was significant when the data for the entire 12-week period were utilized. Furthermore, these two methods of comparison gave parallel results for significance of the drop in mean standing systolic and diastolic pressures of the guanethidine-treated group for the first 6- and for the entire 12-week period of the double-blind procedure. The drop in the mean supine diastolic pressure with guanethidine without a significant change in the mean supine systolic pressure is of interest and, in our opinion, warrants further investigation.

The relatively narrow dosage range found during the 12-week period that comprised this evaluation and the comparable mean pressure responses after six·and 12 weeks of therapy indicate that guanethidine had a fairly constant antihypertensive effect without evidence of tachyphylaxis. The number of serious side effects that occurred with the use of guanethidine were less frequent than those with the ganglionic blocking agents. However postural hypotension, with its associated hazards, obviously can occur as the result of guanethidine therapy, and judicious administration is advised.

Summary

(1) The amidoxime, guanethidine, when given in single daily oral dosage to a group of 20 patients, significantly lowered the standing mean systolic and mean diastolic pressures during the 12-week period of a double-blind study. The supine diastolic mean pressure was also significantly reduced. No significant change in supine systolic mean pressure was noted.

(2) The mean systolic pressures of the guanethidine-treated group during the last six weeks of therapy were 186 mm. Hg supine and 154 mm. Hg standing, as compared with 178 mm. Hg supine and 184 mm. Hg standing for the placebo group.

(3) The mean diastolic pressures during the last six weeks of treatment with guanethidine were 105 mm. Hg supine and 92 mm. Hg standing, as compared with 115 mm. Hg supine and 116 mm. Hg standing for the placebo group.

Acknowledgments

We thank Collin Cooper, Donald Feinstein, Edward Henderson, John Egan, Eli Ginsberg, and George Herron for their participation and help.

We are indebted to J. L. Webb, Department of Pharmacology, University of Southern California School of Medicine, for his helpful suggestions in initiating this study.

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APPENDIX

TABLE 1A
STANDING DIASTOLIC BLOOD PRESSURES
Guanethidine Group (mm. Hg)

Patient	Week						
	0	2	4	6	8	10	12
1	110	120	110	100	93	100	110
2	124	100	100	110	100	100	102
3	110	120	120	118	100	78	100
4	130	110	90	100	90	100	100
5	110	110	65	82	80	70	68
6	110	88	98	104	90	100	85
7	110	104	80	94	72	90	90
8	108	100	80	84	80	98	100
9	120	120	110	110	102	100	105*
10	160	150	112	110	80	90	75
11	110	110	75	94	84	90	90
12	130	90	90	90	80	85	90
13	120	110	95	100	100	80	110
14	120	84	90	70	75	70	80
15	110	128	100	110	80	100	110
16	110	80	50	100	65	90	90
17	140	120	—	—	—	—	—
18	110	108	95	95	100	80	90
19	114	140	130	130	110	130	140
20	120	120	90	90	95	90	90

* Unable to tolerate over 50 mg./day.

TABLE 2A

SUPINE DIASTOLIC BLOOD PRESSURES

Guanethidine Group (mm. Hg)

Patient	Week						
	0	2	4	6	8	10	12
1	100	108	130	130	130	100	112
2	120	98	96	115	92	100	100
3	110	110	110	112	110	98	105
4	130	120	120	110	110	106	110
5	110	110	80	110	90	90	80
6	110	104	110	100	98	110	115
7	100	108	100	102	90	100	120
8	108	100	80	80	90	110	110
9	120	130	118	120	130	120	120*
10	160	116	150	160	130	122	120
11	110	110	80	100	100	90	110
12	120	95	100	110	90	90	95
13	100	120	90	100	105	90	110
14	120	94	90	90	85	90	100
15	130	140	130	160	115	115	120
16	110	110	80	110	80	110	105
17	140	130	—	—	—	—	—
18	100	128	95	85	110	85	100
19	114	146	150	140	130	135	160
20	120	100	95	90	95	90	90

* Unable to tolerate over 50 mg./day.

TABLE 3A

STANDING SYSTOLIC BLOOD PRESSURES

Guanethidine Group (mm. Hg)

Patient	Week						
	0	2	4	6	8	10	12
1	160	160	140	140	210	190	150
2	180	150	160	160	140	140	180
3	160	190	180	196	150	124	160
4	200	152	180	130	140	138	156
5	150	160	100	130	120	115	112
6	170	140	124	128	136	130	150
7	180	160	142	164	140	180	168
8	160	160	135	152	140	140	150
9	180	190	148	160	184	190	190
10	200	220	180	170	90	180	120
11	160	150	108	138	120	120	140
12	200	140	125	120	145	150	136
13	160	160	135	140	175	140	170
14	170	160	175	120	85	110	130
15	200	200	210	180	215	255	236
16	178	155	150	180	170	125	130
17	164	160	—	—	—	—	—
18	190	160	140	180	180	180	170
19	210	190	180	170	140	150	240
20	200	180	140	150	130	160	175

TABLE 4A
SUPINE SYSTOLIC BLOOD PRESSURES
Guanethidine Group (mm. Hg)

Patient	Week						
	0	2	4	6	8	10	12
1	160	170	160	210	230	200	220
2	180	180	160	190	170	170	190
3	170	190	200	210	180	168	200
4	190	160	200	190	180	160	190
5	170	170	130	150	140	160	120
6	155	170	156	150	154	158	170
7	210	210	200	240	230	240	210
8	150	180	150	150	165	170	205
9	200	230	192	220	198	210	220
10	220	240	210	180	200	210	190
11	180	150	128	160	170	150	200
12	190	170	170	140	185	200	180
13	180	210	170	190	210	210	200
14	170	160	130	160	120	120	170
15	240	245	235	240	230	260	230
16	186	186	180	200	170	140	160
17	200	234	—	—	—	—	—
18	180	175	180	175	170	165	170
19	220	240	240	260	215	200	230
20	190	190	200	200	180	195	195

TABLE 5A
STANDING DIASTOLIC BLOOD PRESSURES
Placebo Group (mm. Hg)

Patient	Week						
	0	2	4	6	8	10	12
1	130	140	144	150	130	140	140
2	120	110	140	120	136	130	120
3	110	120	110	118	112	—	—
4	112	110	110	110	95	110	110
5	100	100	110	100	98	98	104
6	108	108	84	100	108	120	105
7	110	110	120	100	105	120	115
8	110	120	109	120	110	—	—
9	140	160	160	170	160	160	—
10	110	100	100	100	90	100	100
11	115	108	110	110	112	110	110
12	108	108	100	115	100	100	82
13	116	110	95	120	—	—	—
14	120	110	130	126	100	110	110
15	110	120	130	120	130	140	110
16	100	115	120	110	110	110	100
17	120	135	130	130	130	—	—
18	110	118	110	110	98	120	110
19	100	100	110	100	100	90	95
20	114	130	130	125	130	120	120
21	120	100	140	100	95	100	—

TABLE 6A
SUPINE DIASTOLIC BLOOD PRESSURES
Placebo Group (mm. Hg)

Patient	Week						
	0	2	4	6	8	10	12
1	150	140	150	150	140	130	140
2	130	115	130	120	110	130	130
3	110	130	110	112	112	—	—
4	108	110	100	100	100	110	100
5	105	110	110	110	90	92	104
6	110	110	98	100	102	106	100
7	110	110	122	110	110	140	110
8	130	130	128	108	140	—	—
9	140	160	160	160	160	160	—
10	120	110	110	110	100	98	98
11	110	100	110	110	100	118	110
12	110	110	100	110	102	100	110
13	120	100	95	120	—	—	—
14	100	100	106	126	105	100	100
15	118	140	124	130	130	160	120
16	110	110	102	110	100	105	110
17	110	120	130	125	120	—	—
18	120	112	110	115	110	120	110
19	100	110	110	115	110	100	90
20	114	150	130	130	110	120	120
21	120	100	140	100	95	100	—

TABLE 7A
STANDING SYSTOLIC BLOOD PRESSURES
Placebo Group (mm. Hg)

Patient	Week						
	0	2	4	6	8	10	12
1	190	210	190	220	180	230	210
2	220	180	188	200	200	210	220
3	160	170	160	172	168	—	—
4	154	150	160	160	128	160	150
5	150	150	170	130	144	142	180
6	180	170	132	160	170	180	165
7	170	170	170	190	160	194	180
8	220	220	210	220	220	—	—
9	170	180	180	200	200	220	—
10	160	140	130	140	122	150	170
11	150	138	160	150	152	140	130
12	200	160	160	180	220	170	168
13	180	180	150	160	—	—	—
14	170	175	190	195	190	170	166
15	162	170	160	150	160	170	130
16	220	210	180	150	180	170	180
17	220	220	210	240	210	—	—
18	190	190	188	190	200	200	230
19	160	142	140	155	130	180	160
20	180	160	196	210	200	210	190
21	235	210	210	210	210	220	—

TABLE 8A

SUPINE SYSTOLIC BLOOD PRESSURES

Placebo Group (mm. Hg)

Patient	Week						
	0	2	4	6	8	10	12
1	220	220	210	240	208	230	240
2	210	220	220	200	230	220	230
3	160	174	170	162	160	—	—
4	162	160	160	150	140	160	150
5	170	180	180	160	142	166	170
6	144	170	160	160	160	180	180
7	170	170	188	198	180	182	200
8	230	210	240	230	220	—	—
9	200	182	210	200	202	220	—
10	180	170	170	190	142	158	170
11	140	138	160	150	152	160	150
12	200	205	200	210	220	200	250
13	220	210	185	180	—	—	—
14	170	200	190	225	170	170	170
15	166	170	164	160	150	150	155
16	180	170	170	160	180	160	170
17	230	232	222	230	230	—	—
18	190	220	190	180	200	250	200
19	160	162	160	185	140	180	180
20	160	180	194	210	185	190	210
21	215	210	210	210	220	210	—

CLINICAL EXPERIENCES WITH BRETYLIUM TOSYLATE

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Bretylium tosylate is a new compound synthesized by Boura *et al.*[1] It has the chemical structure shown in (FIGURE 1). This substance is said to block selectively the peripheral sympathetic (adrenergic) nervous system without antagonizing the effects of injected or released epinephrine or norepinephrine. Such action may make it possible to study the effects of stimuli on chemically sympathectomized animals and on man. The acute effects of this drug given intravenously to man are described elsewhere in this monograph by Conway. The selective action of this drug suggests that it reduces high blood pressure without producing the undesirable parasympathetic side effects of ganglion-blocking drugs. Preliminary reports by Boura *et al.*,[2] Smirk and Hodge,[3] and Soloff[4] indicate that this type of effect is indeed obtained. A more extensive report by Dollery *et al.*[5] suggests that the drug is less frequently effective in patients with fresh retinal hemorrhages or papilledema.

This report summarizes our clinical experiences in the treatment of hypertensive subjects with oral bretylium tosylate.

Materials and Methods

There were 37 subjects (TABLE 1), 24 males and 13 females, 37 to 71 years of age. Twenty-four had been under our personal observation for at least two years; all of these had been unresponsive or intolerant to previous antihypertensive regimens. The others were hypertensive persons who had recently come under our care. All had clinical or electrocardiographic evidence of left ventricular hypertrophy or had roentgenologic evidence of cardiac enlargement. Four had Grade I and 33 had Grade II or III retinal vascular changes (Keith-Wagener classification). Two had fresh retinal hemorrhages. One of these two had congestive heart failure with massive edema of the legs. All subjects were instructed to avoid eating table salt and salt-rich foods.

The initial oral dose of bretylium tosylate was 100 mg. every 8 hours. In hospitalized subjects, each dose was increased by 100 mg. daily until a significant orthostatic hypotensive effect was obtained or significant undesirable side effects had occurred. For outpatients similar increases in dosage were made weekly. Later, with our increasing confidence in the effects of the drug, the initial dose was 200 mg. every 8 hours, and the dose was increased more rapidly. A double blindfold method of study was not used. It was anticipated that the effects of this drug would be primarily orthostatic, so that each subject's recumbent blood pressure could serve as a control of, and reference for, the effectiveness of the drug's action.

The cardiac output, total peripheral resistance, glomerular filtration rate, renal blood flow, and renal vascular resistance of three recumbent subjects were determined before and after satisfactory orthostatic hypotensive effects were achieved. The cardiac output and total peripheral resistance were measured supine and standing in two subjects after orthostatic hypotension had been produced by bretylium tosylate.

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Results

The undesirable side effects are listed in TABLE 2. Only four subjects developed side effects that required discontinuance of the drug. One (H.G.) complained of itching eyelids, which were red. He refused to continue taking the drug because he believed he was allergic to it. Several weeks later he was persuaded to try the drug again. After two doses of 100 mg. each, he developed the same symptoms. In three of the five subjects who had had elevated blood urea nitrogen before treatment, higher levels developed during treatment. Treatment was discontinued. Two of these three were very sick and died three and six weeks later of coronary thrombosis. The third (T.H.) will be discussed below. The blood urea nitrogen of the last two dropped to normal after orthostatic control of the hypertension was achieved. Three developed dyspnea: one (M.J.) is one of the subjects who died of coronary thrombosis, one (L.W.) lost the symptom after three days of orthostatic hypotension, and one (M.R.) complained of fatigue and dyspnea after walking one city block. In the case of M.R., except for orthostatic hypotension, the physical examination remains unchanged. This patient has not yet consented to undergo hemodynamic studies, which may be able to demonstrate the basis of her symptoms. Four patients complained of stuffy noses, four volunteered that bowel movements were freer, and one complained of occipital headaches and cold feet. All these symptoms were trivial and did not require discontinuance of the therapeutic regimen.

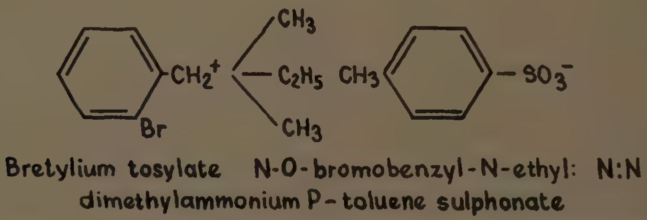
CH3
CH2+
C2H5
CH3
CH3
SO3−
Br
Bretylium tosylate N-O-bromobenzyl-N-ethyl: N:N
dimethylammonium P-toluene sulphonate

FIGURE 1. The structural and chemical formulae of bretylium tosylate.

TABLE 1
DATA ON 37 HYPERTENSIVE SUBJECTS TREATED WITH BRETYLIUM TOSYLATE
24 Males, Age 47–71 yr.; 13 Females, Age 37–68 yr.

24 unresponsive or intolerant to previous regimens
Left ventricular hypertrophy, 35 subjects
Eyegrounds: Grade I, 4 subjects; Grades II and III, 33 subjects
  Fresh retinal hemorrhages, 1 subject (L.W.)
  Fresh retinal hemorrhages and cardiac failure, 1 subject (T.H.)
Elevated BUN, 5 subjects (M.S., S.S., F.S., T.H., L.W.)

All other symptoms were directly attributable to orthostatic hypotension.

Weakness, giddiness, lightheadedness, and fatigue were significant only when orthostatic hypotension was excessive. Otherwise, orthostatic hypotension was unusually well tolerated. On rare occasions such symptoms may be of but momentary duration when orthostatic hypotension is otherwise asymptomatic. We have not been able to determine the cause of these brief effects. Perhaps excessive hypotension is present but too short in duration to be detected once the symptoms have disappeared. These short-lived symptoms cannot be controlled by manipulating the dose of bretylium tosylate without loss of the drug's hypotensive effect.

Orthostatic hypotension was achieved in all subjects but one. This one (T.H.) was a 58-year-old Negro who claimed that he has had high blood pressure for as long as he can remember. He had been under treatment without success for eight years. In November 1959 he became short of breath. He failed to improve on digitalis and antihypertensive regimens and was finally admitted into Tempel University Hospital in severe congestive heart failure. He was orthopneic and his legs were waterlogged. His blood pressure was 202/160 mm. Hg. The eyegrounds showed fresh retinal hemorrhages as well as old exudates and arteriosclerosis. Bretylium tosylate, 1200 mg. every 8 hours, failed to change his blood pressure. Because of his critical condition it was thought advisable to change the treatment to parenteral reserpine and hydralazine and oral chlorothiazide. He slowly improved over a period of two weeks. Congestive heart failure vanished and his blood pressure stabilized at 180/120 mm. Hg. It was the consensus of the ward physicians that improvement was partly spontaneous and partly due to diuresis. After the blood pressure had remained constant for several days, 800 mg. bretylium tosylate 3 times a day produced a prompt drop in the standing mean blood pressure, from 150 mm. Hg to 105 mm. Hg. This effect, however, lasted only five days, and again ascending doses, up to 3600 mg./day, failed to influence the standing blood pressure.

TABLE 2

UNDESIRABLE SIDE EFFECTS OF BRETYLIUM TOSYLATE GIVEN TO 37 HYPERTENSIVE SUBJECTS

Itchy eyelids, 1 (H.G.); drug stopped
Stuffiness of nose, 4 (M.J., A.H., A.H., L.M.)
Free bowel movements, 4 (A.L., A.H., F.S., F.W.)
Occipital paresthesia, 1 (F.W.)
Dyspnea, 3 (M.R., L.W., M.J.)
Elevated BUN, 3 (S.S., T.H., M.J.); drug stopped
  M.I. and S.S. died of unrelated coronary thrombosis 6 and 3 weeks after discontinuing therapy

The effective orthostatic hypotensive dose varied from 600 to 1800 mg. daily and was given in three divided doses. This effective dose could not be predicted. It bore no apparent relation to the height of the untreated blood pressure or to any other finding. It was not related to the severity of the cardiovascular disease.

The average orthostatic hypotensive effects on our first 13 subjects, who are representative of the entire group, are illustrated in FIGURE 2. These effects, however, were not smoothly maintained. There were frequent lapses into low hypertensive levels and, on rare occasions, into almost pretreatment levels.

Supine blood pressure can be lowered if sufficient drug is given to produce intolerable orthostatic hypotensive levels. Otherwise the effect on recumbent blood pressure is insignificant and, even in the sitting position, the blood pressure effect is unimpressive.

It is frequently stated that drugs that reduce blood pressure only in the standing position are of no value in the treatment of high blood pressure. It is possible, however, that reduction of vasoconstriction for but part of the day may be of benefit to hypertensive subjects. Certainly, the lives of subjects with malignant phase of hypertension have been prolonged by the use of ganglion-blocking drugs that are orthostatic hypotensive agents.

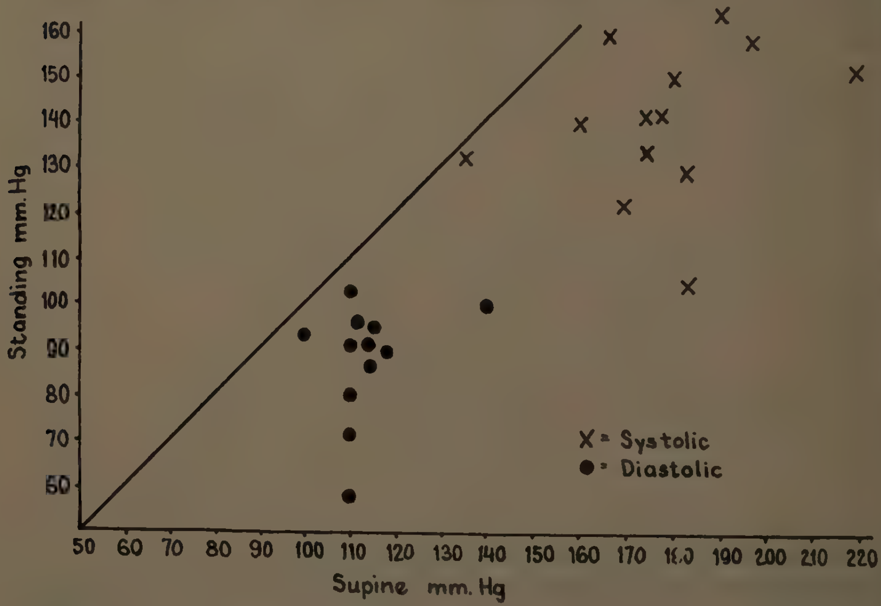

FIGURE 2. The orthostatic hypotensive effects of bretylium tosylate on 13 hypertensive subjects.

However, the orthostatic hypotensive state produced by bretylium tosylate can be converted into the pretreatment hypertensive state instantly by assumption of the recumbent position. Such rapid and wide swings in blood pressure are potentially dangerous for the cardiovascular system. They may be a factor in the increasing incidence of nonsyphilitic aortic aneurysms. For this reason chlorothiazide was added to the bretylium tosylate, in doses of 500 to 1000 mg./day, in an attempt to prevent these swings and to reduce the supine blood pressure. FIGURE 3 indicates that this combination is partly successful. Blood pressures in the supine position, although still in the hypertensive level, are distinctly lower than those present before treatment. Furthermore, the dose of bretylium tosylate necessary to maintain this level could have been reduced from two-thirds to one-third before chlorothiazide was added.

This apparently potentiating effect of chlorothiazide on bretylium tosylate was not sustained over a four-month period. TABLE 3 illustrates this point. Treatment was discontinued in one patient (F.S.) because of a rising blood urea nitrogen. The patient died later of coronary thrombosis. The initial dose of bretylium tosylate necessary to produce an orthostatic hypotensive

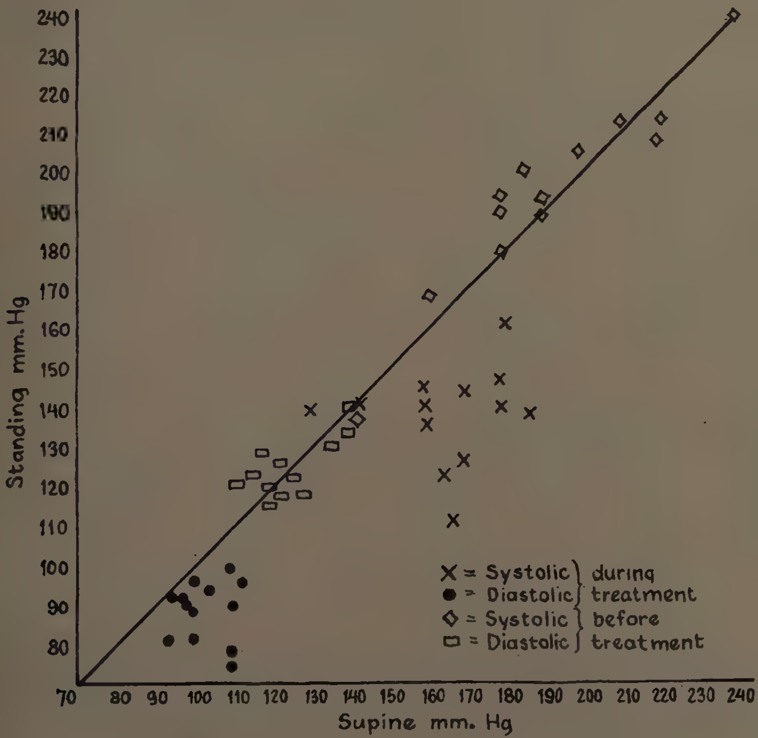

FIGURE 3. The orthostatic and supine hypotensive effects of a combination of bretylium tosylate and chlorothiazide on 13 hypertensive subjects.

TABLE 3

INCREASING RESISTANCE TO ORTHOSTATIC HYPOTENSIVE EFFECT OF A COMBINATION OF BRETYLIUM TOSYLATE AND CHLOROTHIAZIDE

	Daily dose*	Initial	4 mo. later
C.L.	900 mg.	600 mg.	1200 mg.
M.R.	900 mg.	300 mg.	900 mg.
J.F.	600 mg.	150 mg.	800 mg.
F.W.	1500 mg.	900 mg.	2200 mg.
A.H.	600 mg.	400 mg.	900 mg.
F.S.	900 mg.	150 mg.	died

* The minimal daily orthostatic hypotensive dose of bretylium tosylate.

effect was smaller than that required before chlorothiazide was given, but within four months four of the five subjects required doses larger than those needed before the use of chlorothiazide. Actually, one subject previously described (T.H.) developed significant tolerance within the amazingly short period of five days. A common type of development of tolerance is shown in FIGURE 4.

The effects of bretylium tosylate on cardiorenal hemodynamics as determined by simultaneous cardiac catheterization and renal functional study in three recumbent subjects is shown in TABLE 4. The hemodynamic effects of assuming the erect position while under effective treatment with the drug is shown in TABLE 5.

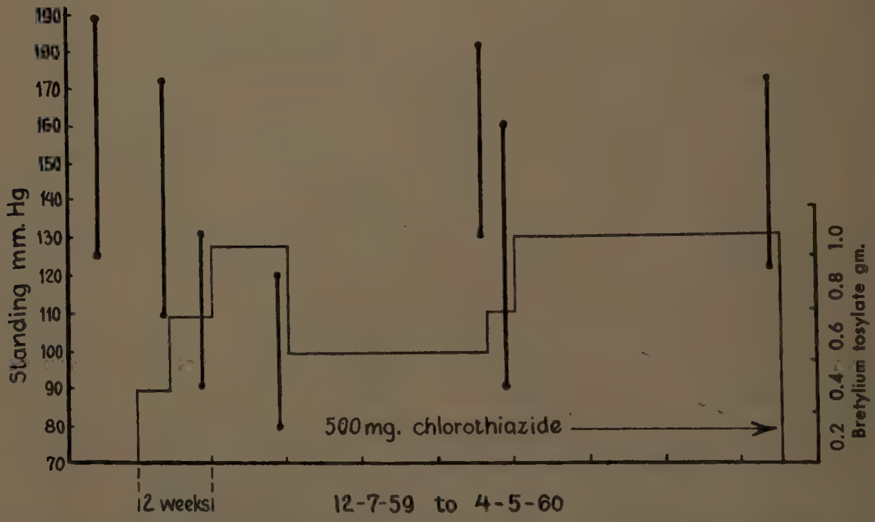

FIGURE 4. The development of tolerance to bretylium tosylate in a 54-year-old man, a known hypertensive for 30 years. Grade II hypertensive retinopathy. No renal disease. Note rapid response to bretylium tosylate, which is accentuated by addition of chlorothiazide. However, after 6 weeks, the dose of bretylium tosylate had to be increased until, after 7 more weeks, the original amount was ineffective in producing orthostatic hypotension. This man had been completely resistant to all previous hypotensive regimens.

Discussion

These observations indicate that bretylium tosylate is a potent antihypertensive drug that produces few side effects other than those due to the lowered blood pressure. This effect is accomplished by blocking the normal increase in sympathetic vasoconstriction when the erect position is assumed. The drug, however, is not an ideal antihypertensive.

Bretylium tosylate may also lower cardiac output slightly in the recumbent position. Simultaneous determinations of the cardiac output by the cardiac catheterization technique and of the renal clearance may yield renal values comparable to those obtained when renal studies alone are done, but the cardiac output may be higher and the total peripheral resistance lower than when cardiac output studies alone are done[6] under basal conditions. However, it is likely that the comparative studies are valid. The mechanism of this effect has not been clarified; it may be a primary myocardial effect. The lowering of blood pressure could compromise renal function and may be the reason for a rise in blood urea nitrogen in subjects with severe renal dysfunction. Such effects are common to all ganglion-blocking drugs that invariably produce undesirable and at times intolerable parasympathetic effects. In this sense bretylium tosylate is superior as a blood pressure depressive agent to all the ganglion-blocking drugs. Its chief disadvantage compared to some of them is the unpredictability of the initial effective dose. This disadvantage may be due to its poor absorption from the gastrointestinal tract.[5] Another disturbing feature of the drug is the wide and rapid swing of blood pressure that occurs with change in body position.

TABLE 4

DATA OBTAINED BY SIMULTANEOUS CARDIAC CATHETERIZATION AND RENAL FUNCTIONAL STUDIED BEFORE AND AFTER ADMINISTRATION OF AN EFFECTIVE ORTHOSTATIC HYPOTENSIVE DOSE OF BRETYLIUM TOSYLATE

Patient	Age	Sex	Date of therapy	Mean BP	Cardiac output (l./min.)	Total periph. resist.[§]	Glom. filtr. rate (cc./min.)	Renal blood flow (cc./min.)	Renal vascular resistance (cc./sec.)
Normal						(<1)	(95–100)	(590–635)	(5.63–6.73)
S.T.	59	F	B[*] 12/10	171	10.7	0.97	74	635	16
			A[*] 1/7	170	6.0	1.70	54	459	21
G.T.[†]	60	F	B 12/10	205	10.7[‡]	1.15	84	601	20
			A 1/7	200	12.3[‡]	0.97	71	594	20
S.B.	53	F	B 12/3	209	8.0	1.57	78		
			A 1/14	220	6.8	1.95	78	577	23

[*] B, before therapy; A, after therapy.

[†] The catheter could not be passed into G.T.'s right atrium.

[‡] Venous blood sample from superior vena cava.

[§] Mean arterial pressure (mm. Hg) divided by cardiac output (cc./sec.).

TABLE 5

BRETYLIUM TOSYLATE THERAPY, PATIENT T.R.[*]

	Supine	Erect
Blood pressure (mean)	150	105
Cardiac output (dye dilution)	9.35, 8.6 l./min.	6.0, 6.0 l./min.
Total peripheral resistance (mm./cc./sec.)	0.96, 1.04	1.05, 1.05

[*] April 29, 1960; 800 mg. t.i.d.

Note failure of peripheral resistance to rise as the erect position is assumed after an effective orthostatic dose of bretylium tosylate. This failure coupled with (probably) the normal decrease in cardiac output accounts for the orthostatic hypotensive effect of the drug.

It is primarily for this reason that bretylium tosylate is not recommended as primary treatment for high blood pressure but only as an adjuvant when a low-fat low-salt diet with saluretic and sedative drugs is ineffective. This combination does produce a more effective hypotensive response and diminishes the wide swings in blood pressure that occur with change in body position when bretylium tosylate is used alone.

Even this combination, however, is associated with a high incidence of tolerance that develops surprisingly rapidly. Perhaps other hypotensive agents combined with bretylium tosylate will be found more effective, and effective for a longer time.

Conclusions

Bretylium tosylate is a potent orthostatic hypotensive agent.

Orthostatic hypotension is produced by blocking increased sympathetic vasoconstriction on standing.

It produces insignificant blood pressure effects in the sitting and supine positions.

It should be used only as additional therapy, when a low-fat low-salt diet with saluretic and sedative agents is ineffective.

When so used its chief drawback is in its high incidence of rapidly developing tolerance.

The possibility of combining bretylium tosylate with other antihypertensive agents to obtain more frequent long-term responses deserves investigation.

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CLINICAL PHARMACOLOGY OF NEWER ANTIHYPERTENSIVE AGENTS, MONOAMINE OXIDASE AND DECARBOXYLASE INHIBITORS, BRETYLIUM TOSYLATE, AND GUANETHIDINE

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It is the purpose of this presentation to consider the clinical actions of several newer agents that possess similar antihypertensive properties. The administration of monoamine oxidase and decarboxylase inhibitors, guanethidine, or bretylium tosylate to hypertensive patients produces a predominantly orthostatic lowering of the blood pressure, which is evidence of sympathetic blockade. Furthermore, this sympathetic blockade is unaccompanied by those symptoms that are indicative of blockade of parasympathetic function: namely, blurred vision, dry mouth, constipation, and impotence. Thus in addition to the contributions such agents may make to understanding the role of the sympathetic nervous system in primary hypertension, these agents also appear to offer the patient with moderate to severe hypertension the opportunity to take a medication with potent antihypertensive properties and yet enjoy daily living free of distressing side effects.

More than adequate prior discussion of the pharmacology and clinical effects of bretylium tosylate and guanethidine permits minimal coverage of these drugs here, although I propose to contrast their advantages and disadvantages with those of the enzyme inhibitors.

Monoamine Oxidase Inhibitors

Iproniazid (Marsilid), first introduced as an antituberculous drug and shortly found to have greater promise in reversing psychic depression, was the first of this still-enlarging group of compounds. It was noted early that postural hypotension was a frequent and undesirable side effect during administration of this agent to psychiatric patients. This fact, coupled with the alterations in metabolism of vasoactive amines resulting from inhibition of monoamine oxidase, intrigued my associates and me, and led to combined biochemical and clinical studies of a number of amine oxidase inhibiting compounds, as already discussed by Sjoerdsma elsewhere in this monograph.

It soon became apparent that iproniazid did not consistently produce hypotension in all patients. Furthermore, at the dose level necessary to produce a hypotensive response (75 to 300 mg./day), side effects soon became quite distressing to the patient, particularly neuromuscular excitability, myalgia, and insomnia. The appearance of hepatic toxicity was noted in addition to these side effects, and caused iproniazid to be removed from further consideration as an antihypertensive agent. However this drug did lead to the concept of applying a new class of pharmacological compounds to the treatment of hypertension.

This concept was further strengthened by the advent of a potent amine oxidase inhibitor, 1-phenyl-2-hydrazinopropane (JB-516, Catron), which when administered to the patient was consistently found to produce hypotension. Clinical studies were extended to hospitalized as well as unhospitalized patients and have been reported fully elsewhere.[1] Eight of 9 hospitalized patients and 10 of 12 unhospitalized patients studied responded with a definite hypotensive effect during the administration of JB-516 alone or in combination with chlorothiazide.

It is significant that no parasympatholytic side effects were observed during JB-516 therapy. The drug was administered to the 12 unhospitalized patients in this study for periods of from two months to more than one year, and no evidence of intolerance was observed. The consistent occurrence of mood elevation was striking and desirable, and was commonly associated with an increase in appetite and a tendency toward moderate weight gain.

However, during administration of JB-516 at higher doses, ranging from 25 to 50 mg./day, six of 12 unhospitalized patients developed a loss of red and green color discrimination. This visual effect was found to be readily reversible upon withdrawal of the drug. Subsequently three patients, two of whom were receiving JB-516 (12.5 mg./day) in combination with hydralazine (Apresoline), and one of whom was receiving increasing doses of JB-516 (12.5 to 62.5 mg./day) in the hospital, developed altered visual fields in addition to the color defect. Immediate withdrawal of the drug resulted in gradual improvement of these visual abnormalities, with complete recovery noted in two patients and minimal optic atrophy resulting in the third. These, then, are three cases of toxic retrobulbar neuritis that has also been found to occur similarly in rare instances during the administration of isonicotinic acid hydrazide at high doses to patients with tuberculosis.[2] These visual abnormalities at higher dose levels of JB-516, as well as two known cases of hepatic toxicity, one of which was fatal, have resulted in curtailment of dosage to levels of 6 to 12 mg./day, which somewhat limits its therapeutic usefulness in hypertension.

As Sjoerdsma has noted, all the monoamine oxidase inhibitors that have been studied in this laboratory have been found to produce postural lowering of the blood pressure, although with certain inhibitors such as nialamide (Niamid) high doses must be employed. Nialamide at high doses has been reported effective in the treatment of hypertension.[3]

At present the only new monoamine oxidase inhibitor that has reached clinical trial in the treatment of hypertension is DL-serine-N^2-isopropylhydrazide (RO-4-1038). This compound is a serine analogue of iproniazid and has been reported by Maxwell to be effective in producing a hypotensive response.[4] However this compound is a hydrazide derivative, and one must maintain a high degree of suspicion with regard to potential hepatic toxicity.

Decarboxylase Inhibitors

As a part of a continuing interest in the effects of altering the metabolism of vasoactive amines, the alpha methyl analogue of dihydroxyphenylalanine (α-Methyl Dopa, MK-350), found to be a competitive inhibitor of the enzyme L-aromatic amino acid decarboxylase, was administered to man subsequent to uneventful chronic animal toxicity studies. The biochemical alterations have already been discussed by Sjoerdsma in these pages. α-Methyl Dopa was administered initially to hospitalized hypertensive subjects. It became apparent immediately that α-Methyl Dopa had an antihypertensive effect, and accordingly the hypotensive response of this agent was studied in ten hospitalized patients with primary hypertension. Lying and standing blood pressures were measured four times daily, and a single average figure in each position was calculated for each day. After a suitable control period on placebo medication (at least 7 days), α-Methyl Dopa was administered orally for periods of 7 to 28 days in single or divided daily doses, ranging from 750 mg. to 4 gm./day.

FIGURE 1 is an example of the orthostatic blood pressure response during administration of α-Methyl Dopa to a hospitalized hypertensive patient. Attention is called to the rapid onset of orthostatic hypotension, marked by the second day of administration. A total of 10 hospitalized patients with primary hypertension were studied in similar fashion. The effect of α-Methyl Dopa on the recumbent blood pressure is shown in FIGURE 2. The top of each bar represents systolic pressure and the bottom represents diastolic. Each solid bar represents that patient's average recumbent blood pressure during the control week of placebo medication; the adjacent hatched bar represents the average pressure during the last 7 days of α-Methyl Dopa administration. It is apparent that the recumbent blood pressure was lowered in 5 of the 10 patients, 4 of these 5 having a milder degree of primary hypertension. Definite orthostatic hypotension occurred in all 10 patients, as shown in FIGURE 3, in the same fashion as described for the recumbent pressure.

Oral absorption studies performed by J. Richard Crout of this laboratory demonstrate that less than 20 per cent of the dose of α-Methyl Dopa is absorbed from the intestinal tract. Peak blood levels are encountered from 2 to 4 hours after oral administration, returning to very low levels within 8 hours and to negligible levels in 12 hours. Patients receiving single daily doses develop a hypotensive response that diminishes in 12 hours and is gone in 24 hours. Thus a dose schedule at 8-hour intervals has been selected for further clinical studies. The dose range of α-Methyl Dopa that has produced the desired hypotensive response has varied from 0.5 to 1.0 gm. three times daily.

During the administration of α-Methyl Dopa to hypertensive patients, effects other than hypotension have been observed. Most prominently, all patients exhibited the transient occurrence of sedation, although this obvious central change disappeared within 24 to 72 hours. Continued administration of the drug seemed to result in more subtle changes of tranquilization in many of the patients. This could not be described as sedation or sleepiness, but rather as a more docile approach to daily activities accompanied by sound nocturnal sleep.

To date 40 patients with various disorders have received α-Methyl Dopa. Three depressive reactions have occurred and were promptly reversed upon withdrawal of the drug. It is interesting to note that two of these patients previously experienced depressive reactions while receiving *Rauwolfia*. In two patients reversible febrile reactions to the drug occurred. One of these reactions was accompanied by transient abnormalities in liver function tests, in-

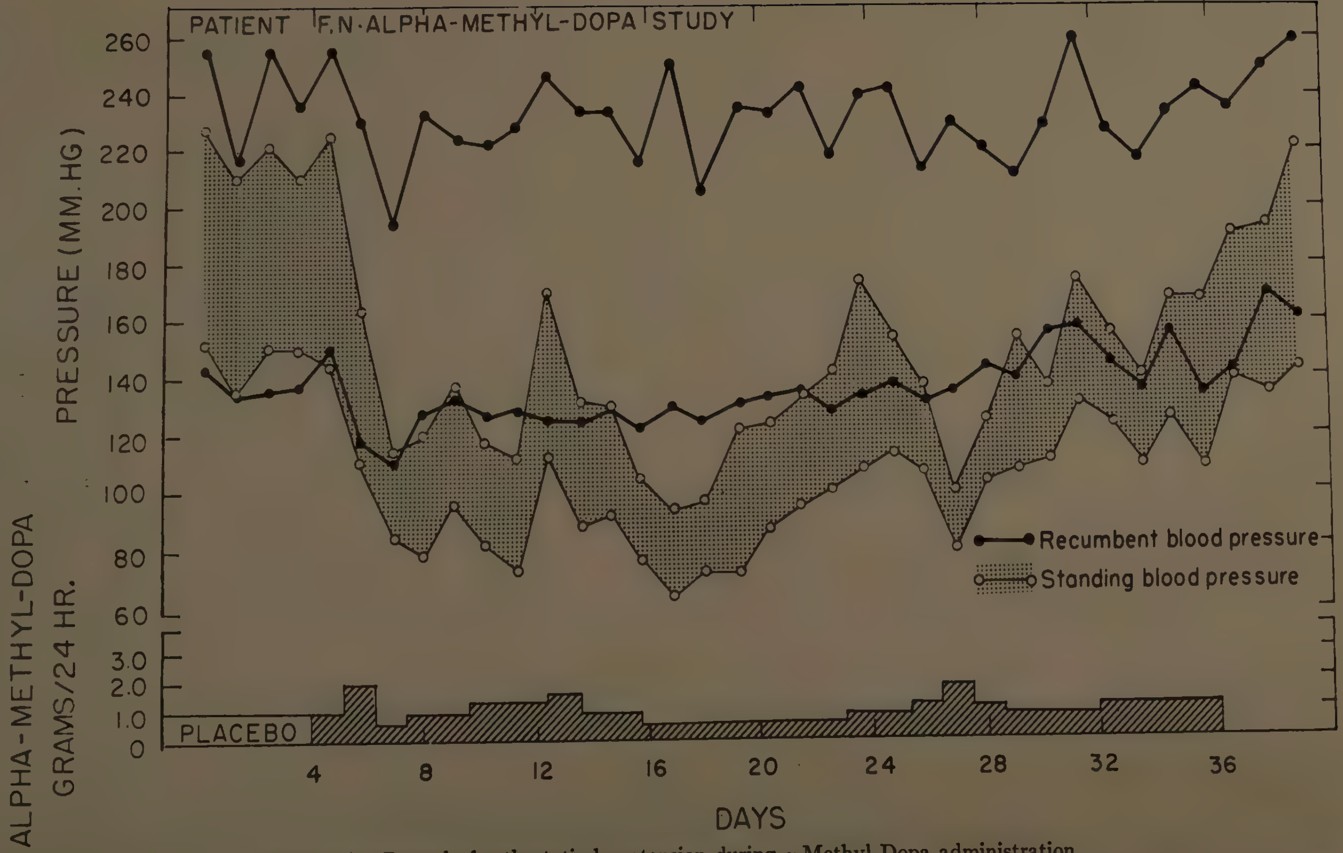

FIGURE 1. Record of orthostatic hypotension during α-Methyl Dopa administration.

cluding elevations of the alkaline phosphatase, serum transaminase, and direct bilirubin in association with a mild increase in circulating eosinophils. These chemical abnormalities recurred without fever upon the subsequent readministration of α-Methyl Dopa. Frequent laboratory assessment for other hematological or chemical abnormalities revealed no further unfavorable findings.

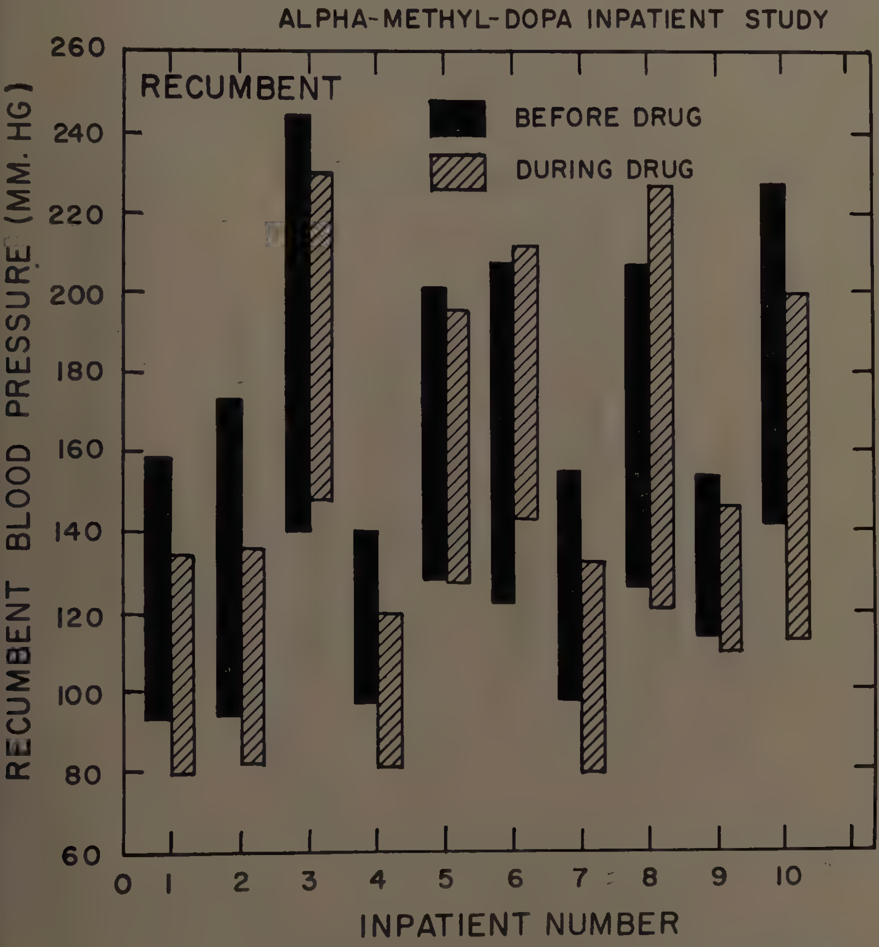

FIGURE 2. Effect of α-Methyl Dopa on recumbent blood pressure of 10 hospitalized hypertensive patients (see text for explanation).

As yet incomplete outpatient studies have demonstrated similar hypotensive effects in all patients. There has been no evidence of intolerance to this agent in 10 patients receiving α-Methyl Dopa for periods of 12 to 16 weeks, nor in one patient who has taken the drug for 8 months.

Since norepinephrine is the transmitter of the sympathetic nervous system, it is a reasonable speculation to relate the consistent reduction of standing blood pressure by α-Methyl Dopa to a reduction in norepinephrine biosynthesis. Although awaiting confirmation, such a relationship provides an attractive working hypothesis for the development of antihypertensive agents on a biochemical basis. Certainly more extensive evaluation of α-Methyl Dopa and related decarboxylase inhibitors seems warranted in hypertension.

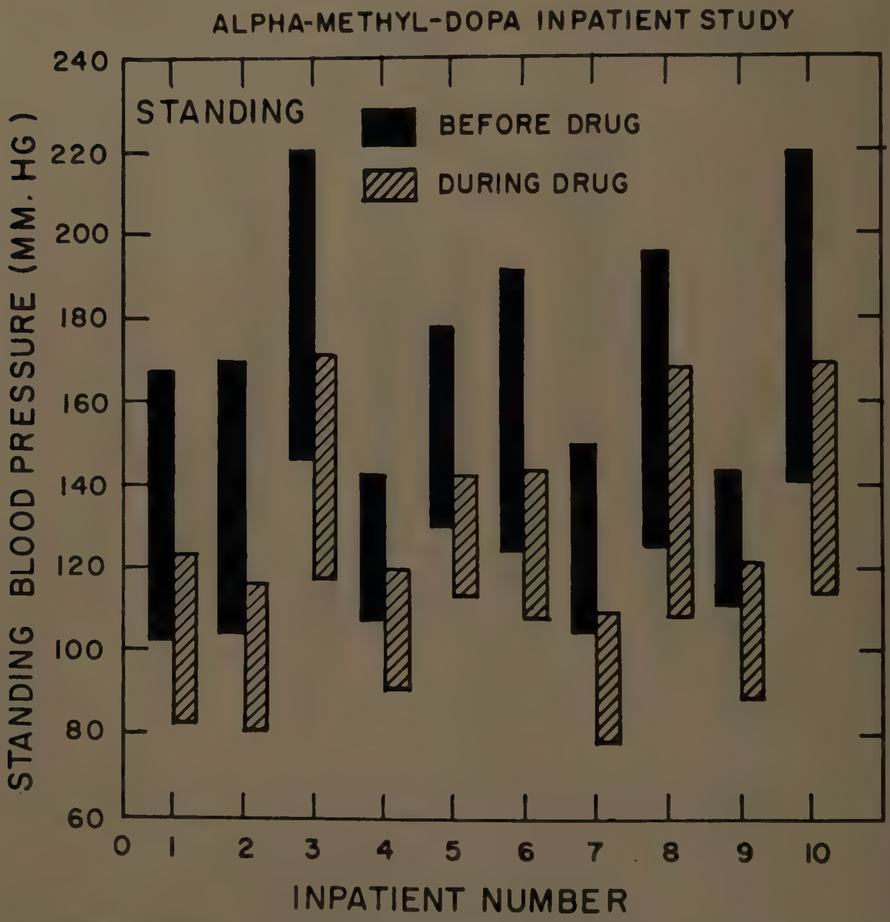

FIGURE 3. Effect of α-Methyl Dopa on standing blood pressure of 10 hospitalized hypertensive patients (see text for explanation).

Discussion and Summary

TABLE 1 is presented to contrast the advantages and disadvantages of the monoamine oxidase and decarboxylase inhibitors, guanethidine, and bretylium tosylate in the treatment of hypertension. Mecamylamine is also included for purposes of comparison. Considering the antihypertensive effects of the various agents, it is apparent that all agents cause postural lowering of the blood pressure and only infrequent and minor lowering of the recumbent pres-

TABLE 1

CLINICAL EFFECTS OF MONOAMINE OXIDASE INHIBITORS, α-METHYL DOPA, BRETYLIUM TOSYLATE, GUANETHIDINE, AND MECAMYLAMINE

	Blood pressure		Undesirable effects			Central nervous system		Duration of action
	Recumbent	Orthostatic	Sympathetic	Parasympathetic	Other	Depression	Stimulation	
Monoamine oxidase inhibitors	±	++++	Delayed ejaculation	± Dry mouth ± Constipation	Visual toxicity (JB-516) Hepatic toxicity (Iproniazid, JB-516)	None	+	Long
Alpha methyl DOPA	Mild ++ Severe ± to +	++++	? Delayed ejaculation		Fever (2 cases) Abnormal liver chemistries (1 case) Depressive reaction (3 cases)	+	None	Short
Bretylium tosylate (Darenthin)	±	++++	Nasal stuffiness	None	Tolerance, variable intestinal absorption	None	None	Short
Guanethidine (Ismelin)	±	++++	Diarrhea Delayed ejaculation	None		None	None	Intermediate
Mecamylamine (Inversine)	±	++++	?	++ Dry mouth ++ Blurred vision ++++ Constipation ++++ Impotence (No erection)		±	None	Short

sure. A possible exception to the latter may occur upon administration of α-Methyl Dopa to mildly hypertensive patients, but more prolonged study of a larger series of patients will be necessary to confirm this initial impression.

In the absence of parasympatholytic side effects, the effects of sympathetic blockade other than alteration of the blood pressure stand out. Of particular interest is the rather common report by the male patient of delayed ejaculation, a physiological function that is under sympathetic control.

Clinical observation of the patient's psychic status during the administration of these agents reveals that neither guanethidine nor bretylium tosylate appear to have any effect on the central nervous system. On the other hand, it is extremely interesting to contrast the stimulation or mood elevation resulting from administration of amine oxidase inhibitors with the tranquilizing or depressing effects that accompany treatment with α-Methyl Dopa. It is very tempting to relate such psychic alterations to alterations in amine metabolism in the central nervous system, and many avenues of investigation of behavioral function are immediately suggested. However, excepting the selective desirability of a modest change in either direction in the mood of hypertensive patients, consideration of such aspects of psychopharmacology is beyond the scope of this investigation. Because of the varied psychic effects of these enzyme inhibitors, appropriate selection of one of these agents in accordance with a patient's pretreatment psychic status should perhaps be considered. The intriguing possibility exists of combining amine oxidase and decarboxylase inhibitors to modify or cancel undesirable central effects while the antihypertensive effect, presumed to be peripheral, occurs.

With respect to the duration of action of these various agents, comment should be directed toward the prolonged action of most amine oxidase inhibitors. A similar, although perhaps somewhat less lengthy, duration of action also can be attributed to guanethidine. A long duration of action of an antihypertensive agent is desirable during chronic therapy, since the hypotensive response may be maintained with only a single daily dose.

To summarize, these agents cause a blockade of sympathetic nervous function unaccompanied by blockade of the parasympathetic nervous system. This represents a pharmacological manipulation of the autonomic nervous system previously not achieved in the long-term approach to antihypertensive therapy. Undesirable sequelae may alter an otherwise unhindered course of one if not all of these agents into the antihypertensive armamentarium. However in the case of the amine oxidase and decarboxylase inhibitors, one must remain optimistic when the collateral understanding of biochemical mechanisms, as well as of the more pure pharmacological actions, are among the results of such clinical investigations. Further studies must be pursued, with particular reference to mechanism of drug action and to the evaluation of analogues of some of the agents discussed here.

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Discussion of the Paper

Marvin Moser (*Montefiore Hospital, New York, N. Y.*): We are all indebted to Gillespie and his co-workers for their excellent investigative work with the amine oxidase and other enzyme system inhibitors that are related to the metabolism of vasopressor amines. In discussing his paper on the action and uses of some of the newer antihypertensive agents, I shall confine my remarks to the drugs with which my associates and I have had some experience during the past year and a half.

We have not used guanethidine or any of the decarboxylase inhibitors. Our experience with bretylium in a group of moderately severe to severe hypertensive patients has been similar to that of others. Bretylium is a potent peripheral sympathetic blocking drug which, unlike some of the earlier agents in this group, such as dibenzylene, also is capable of blocking the cardiac accelerator fibers. Consequently, a compensatory tachycardia does not develop following blood pressure lowering. The drug is poorly absorbed, and this may account for its erratic blood pressure action. In some patients we have been able to eliminate completely ganglion-blocking agents and substitute bretylium with good results. In others who have ceased to respond to ganglion blockers, bretylium has produced a blood pressure response. The effect of the drug on blood pressure is mainly an orthostatic one; we do not believe that bretylium will produce a satisfactory therapeutic result in most patients when utilized alone. In combination with other antihypertensive agents, however, bretylium has been of value. Side effects are minimal. Continued evaluation would appear to be indicated.

We have studied approximately 50 patients utilizing various amine oxidase inhibitors. We have not used JB-516 (Catron), but we have evaluated nialamide (Niamid), RO-5-0831/1 (Marplan), and DL-serine derivative of iproniazid, RO-4-1038. Our experience with nialamide in dosages up to 300 mg./day has been disappointing, and although some definite effects upon emotional activity have been noted, blood pressure response has been poor. In contrast, RO-5-0831/1 and RO-4-1038 have proved to be moderately potent blood pressure lowering drugs in the majority of patients treated. The effect is mainly orthostatic, but some lowering of pressure in the recumbent position has also been noted.

In a series of 30 continuously hospitalized patients with blood pressures of 183.3/100.8 during the 6-week control period, the use of RO-5-0831/1 in dosages of between 30 and 80 mg. daily in 4 divided doses (average of 40 mg.) produced a mean blood pressure fall in the sitting position of −34.1/−18.2 to levels of 149.2/82.6 over a six-week period of time. In combination with chlorothiazide (1 gm./day) the blood pressure fall in another group of patients was even more striking (mean fall of −43.6/−31.8 mm. of mercury).

In an effort to determine whether the effect of reserpine would counteract or supplement the effect of the amine oxidase inhibitor on blood pressure, another group of patients was studied utilizing the two drugs alternately and/or in combination in six-week periods. Results indicate that in this group of patients reserpine (0.5 mg./day) was a poor antihypertensive agent, with an insignificant fall in pressure resulting over the treatment period. When RO-5-0831/1 was added to reserpine, a mean blood pressure fall of −35.8/−19.3 mm. of mercury occurred over a six-week period. Blood pressure response to the MAO inhibitor occurred between the fourth and the fourteenth day after addition of this drug. Blood pressure effect persisted throughout the period of combination drug treatment, and gradually rose following placebo substitution over a period of between seven and 27 days.

In a group of patients who received reserpine, followed by the MAO inhibitor plus reserpine, followed by reserpine again, a secondary blood pressure rise also occurred, although this appeared to occur sooner than when placebos were instituted after the combination had been stopped.

It is a paradox that blood pressure lowering is achieved with the MAO inhibitors, since inhibition of the enzyme systems connected with the breakdown of pressor amines (serotonin, norepinephrine, and epinephrine) results in an increase in pressor amine activity. Another explanation may have to be found to account for the antihypertensive activity of this group of drugs. It has been demonstrated that MAO inhibition can occur without observable blood pressure effect and vice versa. It is of great interest to observe that the combination of reserpine and MAO inhibitor therapy produced a blood pressure lowering. If we assume that the effect of reserpine upon blood pressure is the result of its ability to *decrease* the amount of pressor amine in the periphery, it would suggest this drug might counteract the effect of the MAO inhibitor. This has not been the case in our experience.

Although much remains to be learned regarding the exact action of the MAO inhibitor drugs, they appear to be useful as antihypertensive drugs, especially in combination with chlorothiazide derivatives.

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